UNIVERSITY OF CALIFORNIA SAN DIEGO

Biology and Pedagogy: From Public Outreach to Training Future Experts

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by

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The Dissertation of Rebecca Anne Hardesty is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

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DEDICATION

This dissertation is dedicated to my parents, Beth and David Hardesty. Thank you for believing in me.

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ABSTRACT OF THE DISSERTATION

Biology and Pedagogy: From Public Outreach to Training Future Experts

By

Rebecca Anne Hardesty

Doctor of Philosophy in Communication (Science Studies)

University of California, San Diego, 2019

Professor Morana Alač, Chair

This project focuses on the everyday practices of a neurobiology laboratory and how pedagogical communication is central to its epistemic accomplishments. I contextualize this research by beginning with the national efforts of biologists in the United States during the 1970s to educate the lay public on the significance of biomedical research. Through historical research on the Salk Institute's initiatives on the relevance of biology to social issues, I show that an ethical imperative emerged after World War II within biology to educate the lay public on scientific advances. Drawing a contrast with the present moment in which there is a perception of less public confidence in biomedical research and less effective public communication, this

project answers the question: to where have biology's training and outreach efforts gone if not to largescale public outreach? To answer this question, I conducted a three-year participant-observer study of a lab which uses mice as models of the genetic underpinnings of the cognitive components of conditions such as Down syndrome and Alzheimer's disease. By studying how lab members train junior members, I show how their standards for knowledge production give epistemic significance to their interactions with each other and with their field. The three standards on which I focus are for: making adequate animal models, their material construction, and evaluating their objectivity. By examining moments of instruction, I show how these standards are remade and negotiated through ordinary discursive and material practices. I also argue that biologists' belief that they had a moral imperative to communicate the significance of their work to the lay public did not disappear after the 1970s. Instead, I show that this commitment to education has transformed into contemporary biologists treating the training of novices as part of the epistemic work necessary for making knowledge claims. However, I contend that these cases illustrate how the technical demands of professional biology make it difficult for practitioners and the lay public to have shared understandings of science. This project concludes by discussing how collaborations between biologists and philosophically-informed social scientists can give rise to approaches that can promote greater public understandings of science.

Chapter 1

Introduction

1.1 Argument and Chapter Summary

This project attempts to respond to concerns about conducting work within science and technology studies (STS)[1] in a time when there is a perception that the authority of science has waned. This dissertation takes as its starting point two motivations in STS: to critically understand scientific practice and to make a positive intervention. A core problem that has emerged in the present moment that is related to science skepticism is the perceived lack of effective communication on the part of scientists. I focus here on biologists and biology that applies to medical research and practice. I do so, in part, because biologists in the United States have historically been concerned with educating the lay public. The perceived lack of large public outreach initiatives organized by biologists in the present moment drew my attention to their educational efforts and challenges they currently face.[2] In this project, I examine the

[1] What is STS? The acronym can refer to the interdisciplinary field either called "science and technology studies" or "science, technology, and society." There are many ways of defining this field and explaining its aims. It's diversity of methods, theoretical frameworks, ontological commitments, and sources of methods makes it difficult to provide one description that accurately captures all the scholarship in this field. In this project, I use "STS" in the following way. From the outset, I lean very heavily to the "science" side of science and technology studies. In particular, I align myself most with those in the tradition of laboratory studies or ethnographies of science. This means, my approach is site-specific and concerned most with the everyday practices of scientists. From this position in the field, I would define STS as an interdisciplinary field that studies science as a social endeavor which aims to make the world intelligible. I see STS as a field which examines each item in the previous sentence using a variety of methods (historical, sociological, anthropological, philosophical, etc.) and pursuing varying degrees of critique. These degrees of critique range from that of scientific realism (i.e. the absence of critique) to aspects of critical theory (i.e. feminist STS, post-colonial, Marxist, deconstructionist, etc.).

[2] I want to draw attention to three things in this sentence.: 1) I am not making a claim about the reality of there being a lack of large public outreach initiatives. I mean to draw attention to the *perception* of this. That there is a perception of less scientific literacy and confidence in the lay public is supported by Metz, Weisberg, & Weisberg (2018) and Vernon and Woolley (2019). 2) By lay public, I mean to refer to a large population including the educated but non-scientific experts as well as those with less education. While there are presumably *more* individual

outreach and training practices of biologists at the Salk Institute in the 1970s and of those in a neurobiology laboratory in the present moment (2016-2019). In the course of doing so, I address and provide answers to the following questions: 1) What happened to the emphasis on communication that motivated the large-scale biological research outreach initiatives of the 1960s and 1970s? 2) How do contemporary biologists use communication as a means of producing their epistemic accomplishments – particularly their standards?[3]

This dissertation primarily focuses on biologists' standards in their everyday work and how they are enacted and met through communicative acts. I define standards as the means to construct "uniformities across time and space through the generation of agreed-upon technical rules" (Timmermans and Epstein, 2010).[4] This definition is inevitably broad and covers technologies of infrastructural design, terminology, performance, and procedures (Busch, 2011; Timmermans and Berg, 2003, p. 24–27). Standards are often based in local settings, but they can

efforts dedicated to science outreach presently (in 2019), there is a question regarding their reach and who is conducting them. While there are popular sources of public science education, such as Science Friday broadcast through NPR, the Science Channel, and print and televised science journalism, these all presume a degree of awareness, pre-existing interest, and education. For example, 54% of NPR's audience is college educated compared with the national percentage of 29%. Additionally, NPR listeners tend to be in a higher economic bracket than non-NPR listeners (43% of NPR listeners make over an annual income of $75,000 compared to 26% of non-NPR listeners who make the same amount). To summarize, while there are presumably quantitatively more science outreach efforts at present than there were in the 1970s, they reach a smaller percentage of the US's population. 3) I mean specifically to refer to outreach efforts conducted by *scientists* – not journalists, not public relations experts, not communication experts hired by labs.

[3] My use of the word "accomplishment" or, later, "achievement" is meant to be broad enough to refer to not just the material products, or the materiality of the products, of biology. I use these words to talk about instances where lab members meet their goals, where the goal is not attaining some state of being or merely overcoming an obstacle. For example, I do not use the language of accomplishment or achievement to refer to the lab members avoid some practical obstacles, such as not being able to work with a particular mouse. Instead, I would use it to talk about what they did since they were not able to use a particular model. I use these words to draw attention to the positive or additive things they do to overcome an obstacle. In related cases, I would not call the mere completion of a lab meeting to be an achievement, but I would give this label to the coordination of lab members to convey and teach a field-wide standard to a junior member who then deploys that standard in their speech. In this case, I draw attention to an immaterial product that was not present before the coordinated actions of the lab. In all these cases, I do not use the label of "accomplishment" or "achievement" for everything thing added in a lab meeting. For example, I would not call one lab member passing a cold around an achievement. Instead, following the matters of concern in the lab, I only apply these designations to the products of communication (including speech, publications, experimental design, models, etc.) to what happens when the goals of the lab members are met or what happens on their way to being met.

[4] See also Bowker and Star 1999.

facilitate the coordination of activities across distances. They are created and maintained often through technical experts, professional organizations, the state, and manufacturers (Lampland & Star, 2009). I also use the word to mean "a set of instructions specifying how something will be done" and that "they play an important role in the transfer of knowledge from one location to another" (Zimmerman, 2008, p. 632).[5]

In chapter 2, I take as my starting point the national efforts biologists made in the United States during the 1970s to educate the public on the significance of biomedical research. Through historical research on the Salk Institute's initiatives to communicate the relevance of biology to social issues, I show the ethical imperative that emerged after World War II within biology to educate the lay public on scientific advances. This is based on historical research conducted in the Mandeville Special Collections using the Jonas Salk Papers. Specifically, I focus on the Salk Institute's Council for Biology in Human Affairs and its activities to develop outreach programs that would educate lay audiences and transfer authority of governing biological research's direction to the lay public

In chapter 3, I begin by describing how the Human Genome Project marked a turn in the focus and scale of biology as a field. I describe how the field became increasing specialized around animal models that were genetically standardized. I argue that the complexity of biological research after the Human Genome Project made it increasingly difficult for biologists to communicate with each other across their different animal models and subfields. The specialization of models and techniques poses challenges to instructing novice biologists who both need to master a technique and model while also being able to communicate this to others in their broader field. This chapter presents a case in which the lab members position a new genetic

[5] See also Berg, 1997; Edwards, 2004; Porter, 1995

mouse model they have developed as the gold standard for all mouse models in Down syndrome research. I argue that the members of Lab X setting this mouse as a standard, which they also try to meet, is both an epistemic and communicative accomplishment. By justifying that their own work meets this standard they have set, I show how this lab: 1) tries to move their field toward meeting one of the Human Genome Project's goals of doing research that illuminates human genetic conditions; and 2) attempts to bridge the distance between the specializations within the Down syndrome research community by offering their mouse as the ultimate tool.

Chapter 4 presents two cases in which senior lab members are instructing an undergraduate and a graduate student on how to turn a mouse into a model through material activity. I argue that Lab X gives value to material work in a way that establishes standards for how to use models and evaluate their adequacy. I contend that for this lab, the physical activity of conducting an experiment with an animal turns it into a model. This standard for adequacy is so foundational to this lab's epistemic work that it can be found in the instructions of the most basic and mundane procedure the lab uses daily. Through this chapter, I show how this standard emerges in the interactions between senior and junior members during moments of instruction.

In chapter 5, I describe how Lab X conveys its standards for objectivity to its junior members while training them to design and assess experiments. I reveal that in the course of their work with models, the lab members discursively constitute mice and their neurons as subjects. These subjects have authority over knowledge about the conditions the lab members see the biological material as representing. I argue that, for Lab X, "subjectification" is necessary for them producing claims or models which they regard as objective. This provides an account of scientific objectivity which is intentionally situated and involves constituting biological objects as speaking subjects.

I conclude this dissertation with a final chapter that pulls the threads of the project together. I offer my interpretation of what happened to the perceived moral imperative of biologists in the 1970s. This perceived moral imperative to communicate the significance of their work to the public did not die but was transformed and seeped into the material and epistemic practices of post-Human Genome Project biological research. A key area in which the communicative nature of scientific practices emerges is in the contemporary pedagogical practices that occur in laboratory settings. I return to how central training students is to the epistemic accomplishments of Lab X. I argue that this kind of training enables professional biologists to use material and conceptual tools to make sophisticated claims about human genetics. However, this training makes the biologists so deeply and narrowly specialized that it is difficult for them to communicate the significance of their claims to lay audiences. I conclude by offering two means by which STS scholars can help bridge the gap of understanding between professional biologists and the lay public: one concerns science education, the other concerns interventions to improve everyday understandings of science.

1.2 Post-Truth and STS

This dissertation is ultimately about a single neurobiology lab and its members' attempts to communicate about how to make claims about the natural world. They did this when they trained their undergraduate and graduate students to perform basic procedures, design experiments, and assess the experiments of other labs. They also did this when they published papers arguing for a new standard by which facts about the world could be determined in their

field. And they did this when they allowed me, a philosophically-informed social scientist, to participate in their lab meetings for three years.

As with most laboratory studies, this project is enriched and limited by the locality of its methodology of participant observation. Additionally, as was the case for the earliest lab studies, this work is ethnomethodologically-inspired in the sense that it is guided by the concerns and activities of the lab members on which it focuses. A consequence of this is that it is most readily able to delve into the emergent significance of the mundane interactions between individuals. This can create a rather myopic perspective which limits how much of the world outside of the lab, or even a particular interaction, can color an analysis. However, in November 2016, the world in which my lab had always been embedded smacked into this project. Generally, I would imagine, presidential elections themselves do not shake up scholarship-as-usual so much. This time was no different. Instead, it was what this event revealed about the past and made possible for the future that shook my site, STS, and this project.

In the context of my site, which I will called "Lab X," questions immediately emerged. Would this impact what kinds of research would be funded? A promising, and previously highly fundable, area of their research involved vaccines. Would they receive less federal funding for that? Would this constrain them to the specific interests of private funding agencies? What about visas? Eight out of the twelve lab members who were most centrally involved in the lab's projects were not United States citizens. At least two students were from countries that would end up on executive order "Protecting the Nation from Foreign Terrorist Entry into the United States," also known as the "travel ban." Would they be affected?

In STS, concerns also emerged – first on a personal non-professional level and then, more slowly, on the level of the profession. In the 2016 joint meeting of the Society for the Social

Studies of Science and the European Association for the Study of Science and Technology in Barcelona at a gathering on the beach, over a dozen junior and established STS scholars sat around catching up after the day's panels. Two topics of the evening were the likelihood of "Brexit" actually going through and the chances of Donald Trump being elected. Both ideas, while perplexing to the gathering's attendees, were dismissed as highly unlikely. In the months after, at subsequent conferences and in emails, the group from Barcelona expressed worries. The US scholars were worried about their National Science Foundation funding and the UK scholars, many of whom were from other European Union countries, became worried about their postdoctoral positions. However, the largest concern was regarding how we were so wrong and, perhaps, ignorant of the views and experiences of a significant portion of the populations of voters.[6]

On the level of the discipline, STS scholars described the results of the 2016 election as signifying the triumph of "post-truth" politics. What post-truth politics meant for STS, "a field centrally concerned with the authority of epistemic institutions and the epistemics of authoritative institutions," became a problem for its practitioners to address (Jasanoff, 2017). A central concern has been whether STS's critical approach to the studying science is appropriate given concerns that that the authority of science is in doubt. To some practitioners, the 2017 March for Science represents a widespread perception of the "radically altered relationship between science and power." This was the language of a call for papers for a workshop titled Questioning Science in Uncertain Times at Ohio State University." The objective of this

[6] Upon immediate reflection, of course we were ignorant. While fairly diverse in our countries and states of origin, our group was homogenous in key ways. All but one of us were white. Everyone there had, or was on their way to having, a doctorate. Despite race and gender in science and technology being a common topic for the members in that group, no one's career had been significantly challenged or stymied by their racial and gender identities. We also had mobility, each one of us being from universities that happily paid for our travel to, and attendance at, the multi-day conference.

workshop was to address concerns that question "the value and legitimacy of STS scholarship, given its thoroughgoing skepticism of scientific authority, and generate concerns about ceding the public sphere to entrenched private interests and traditional prejudice" (Bhadra, 2017). The workshop sought to determine the value of critiquing science given its present "embattled" state. Additionally, its organizers sought to determine what the role of STS scholars should be in this time of uncertainty. If the trend in STS has been to interrogate or challenge science's exclusive claim to objectivity and fact-production, what projects can there be if the lay public is itself questioning the authority of science?

This last question has been an uncomfortable concern in STS circles and has been the undercurrent in a series of articles both in the popular press, the flagship STS journal, and at least one book. In December 2016, Steve Fuller wrote an article for *The Guardian* and then one shortly thereafter for the blog *Social Epistemology Review & Reply Collection*. In both articles, Fuller makes the idea of "post-truth" his focus. Referencing the *Oxford Dictionary*, he defines it as "relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief" (Fuller, 2016). In his blog post, he dates concerns about post-truth to the science wars, which began shortly after the Cold War ended. This time heralded a reassessment of public funding for science. While Fuller does not discuss it, the Cold Ware funding infrastructure was used to officially start the Human Genome Project, leading to significant changes in the practices and standards of the biological sciences. Fuller points to Latour's move to extend the Edinburgh School's commitment to using the same kinds of explanations in cases of both successful and unsuccessful knowledge claims. In other words, sociologists within the "strong programme" treated claims that were later determined to not be facts the same way they treated ones that were regarded as facts. According to Fuller,

Latour extended this symmetry principle to not cover just explanations, but the objects of explanation themselves.

Fuller continues by claiming that this has gone further than Latour intended. Now, there is symmetry between the actors making these explanations, regardless of the traditional epistemic standing associated with these actors' training or sources of evidence. This last extension of the symmetry principle has resulted in its "universalization." Fuller believes that Latour would have thought that such a universalization would have placed STS as the "central node in a universal network of those studying 'technoscience'" (Fuller, 2016a). However, this is not the case. Instead, "everyone started to apply the symmetry principle for themselves, which led to rather cross-cutting networks and unexpected effects, especially once the principle started to be wielded by creationists, climate sceptics and other candidates for an epistemic 'basket of deplorables'" (Fuller, 2016a). To spell it out, Fuller sees those skeptical of science as using a tool of STS, the symmetry principle, not to interrogate or deconstruct what made something "a fact," but to proclaim what facts are themselves while rejecting the sciences' claim to objectivity.

Fuller concludes his position stating that a post-truth world was inevitable with the democratization of epistemic tools. STS has made accessible its methods of analyzing how knowledge is produced and its social contingencies. Doing so has effectively provided methods for everyone to do so as well. This removed the stability that science provided over what counted as facts. He acknowledges that while this destabilization can be destructive, it is where STS has found itself. In a final repartee, he claims that Latour's subsequent move to reclaim scientific facts as "real" facts through metaphysical analyses amounts to a tactic to undemocratize STS. Instead of trying to save the epistemic authority of science through STS's own power to dictate

historical narratives, Fuller thinks the field ought to "embrace [its] responsibility for the post-truth world" (Fuller, 2016a; Fuller, 2016b).

It was this last joust about STS claiming responsibility for the post-truth world that was the target for Sergio Sismondo's Feburary 2017 editorial in *Social Studies of Science*. In this response, he rejects Fuller's suggestion that STS take responsibility for causing the post-truth moment with its commitment to epistemic democratization. Sismondo believes epistemic democratization must "involve more equitable political economies of knowledge… If the post-truth era starts by blowing up current knowledge structures, then it isn't very likely to be democratization, and in fact most likely leads to authoritarianism" In this response, it appears that Sismondo would contend that while the contents and producers of knowledge ought to be equitable, the traditional structures of knowledge are non-negotiable. His main example of what is "blowing up" current knowledge structures is Twitter, which he rejects as having the authority to "make what we have been calling knowledge" (Sismondo, 2017, p. 3). However, taking Fuller seriously, I think he would argue that the structures of knowledge production have also been put into question by the post-truth movement as well. If the structures of knowledge production are those of peer review, scholarly publication, journalistic publication, and use of evidence produced through the rigorous processes of technoscience, then those too have been levelled by the universalization of the symmetry principle.

Michael Lynch waded into this debate by publishing an article in *Social Studies of Science* in August 2017 outlining both Sismondo's and Fuller's positions. While he provides a more thorough and charitable analysis of Fuller's blog post, he too remains unconvinced by Fuller's claim that STS bears responsibility for the post-truth movement. "Many of us in STS are concerned about selective uses of scepticism to foster political action or inaction, but it is the

height of hubris to suggest that our field gave rise to, or is otherwise responsible for, the rhetorical means through which controversies have been 'manufactured'. If STS is to be credited and/or blamed for the 'post-truth era', a more convincing case needs to be made" (Lynch, 2017, p. 597).

I agree with Lynch that a convincing case needs to be made if one wants to claim that STS is responsible for the post-truth era. However, neither his or Sismondo's responses address the issue of what STS scholars ought to do: a) with respect with critique of science and b) about preserving the authority of science which Lynch, Sismondo, Latour, and Fuller all want to do. Turning specifically to how the November 2016 elections impacted my project, one of my goals is to address the first point. I do so by answering a question that emerged in the course of my lab study: what can it mean to do a laboratory study now and what are ways in which an STS scholar can productively relate to science? While in the lab and during the development of this project, I encountered the same methodological obstacle that was at issue in the Ohio State University workshop. Can a laboratory study still be valuable if there is a growing public perception that laboratories are not *the* determiners of facts? Another question I found myself asking while doing my fieldwork was: on what ought I to focus? Should it be on the ways in which established social categories affect or emerge through scientific practice? Or perhaps I should focus on how what the lab members do *actually* gets to *reality*. While these are all perhaps worthwhile questions to answer, they themselves did not respond the central motivation of studying science informed by concerns about the "post-truth" era while maintaining STS's avoidance of getting into metaphysics.

A source of frustration turned out to be that which dictated the questions that guide this project, the theoretical apparatuses I bring to bear, and the avenue through which I respond to STS's concerns about studying science in a "post-truth" era.[7]

1.3 Matters of Concern and the Epistemic Level of Analysis

When observing the dissemination of misinformation about the safety and necessity of vaccines as well as the reality of climate change, I found myself wondering why there were not large educational campaigns put on by scientists to educate the lay public. For example, members of Lab X had the ability to explain in detail why the vaccines they were testing were effective and safe. In fact, these were their exact topics of study when it came to studying vaccines. Additionally, the lab members were quite good at communicating highly technical topics to the novice. I had observed multiple graduate students come into the lab in their third or fourth years knowing almost nothing about the specific field in which Lab X worked and emerging three years later with expertise on a particular topic. Wouldn't these scientists who were devoted to training novices be able to do so on a larger scale? I was vaguely aware, prior to

[7] This project does not offer a deeper argument about the issues at play for STS in the "post-truth" era, however, I will offer my view on one issue without argument. This issue is the epistemic significance of localist methodologies. Some STS practitioners use localist methodologies that allow them to see something about science that they normally would not be able to see otherwise *and couch it as such*. That is, this is a methodological perspective and could be considered methodological relativism. There are others, including anti-science skeptics, that take localist methodologies as means of making general claims about shared reality. In these cases, methodological relativism is transformed into epistemological relativism. An issue for STS is that these methodologies do not contain a feature which precludes a move toward epistemological relativism. This is precluded through practitioners' own analyses of their data and discussions thereof. This creates a precarious situation for STS practitioners who want to refute an "alternative fact" about the reality of climate change. Epistemological relativism precludes one from making a claim that is superior to another from a different system of evidence and justification. Methodological relativism does not close off the possibility of there being "Truth;" however, it is an unsettled question of how to get to it from a localist perspective. This project does not advance a theoretical argument of what would be the best way out of this situation. Instead, I offer an approach that takes on my participants' commitments to reality and explores their justification. In this way, my project here leaves the untouched the epistemic authority of scientific facts and uses localist methods to see how their creators' systems of justification maintain themselves through everyday practice.

conducting historical research, that there had been initiatives in the 1970s in which biologists attempted to do public outreach. Where had those initiatives gone?

Examining contemporary journalistic pieces on health and science research, journalists often cast themselves conveyers of information. Charles Briggs and Daniel Hallin describe how even though health journalism portrays itself as passively presenting scientific information to the lay public, they are doing much more than that. These journalists play a performative role in their work by making particular biomedical findings significant in everyday life. The stories enforce who has authority over health information, how a patient ought to be, how scientific or health research is part of a particular social movement, etc. They shape the phenomena on which they report making them incredibly powerful social devices (Briggs & Hallin, 2016). However, notably, these stories are written by journalists and not the scientists who conduct the research.

This is understandable because journalists are trained to communicate with the lay public whereas one might think that scientists are not terribly concerned with public outreach in their everyday work. However, in the course of my participant observation, I became aware that the lab members were concerned with communicating effectively to an audience broader than their peers in the same lab. The senior members of the lab were invested in teaching the junior members to assess experiments and approach biological research as members of their profession. The lab was also concerned with making its research intelligible to those outside of the lab within and outside of its immediate field. In the course of attempting to determine why the members of Lab X, and the members of their field, were not communicating their research to the lay public despite their commitment to training novices, the theoretical frameworks that shape my project solidified.

Perhaps unsurprisingly, the concerns I had about critical approaches to studying science in a post-truth era had already been anticipated by none other than a pioneer of the genre, Bruno Latour. In Latour's paper, in which Fuller says he "famously waved the white flag in the Science Wars," Latour articulates the dangers of critique (Fuller, 2016a). In this paper, Latour reveals parallels between his own focus on showing "'the lack of scientific certainty' inherent in the construction of facts" and those of Republican strategists, with whom he disagrees, pointing to a "lack of scientific certainty" as a reason to dismiss concerns about climate change (Latour, 2004, p. 227). Unlike Fuller in 2016, Latour in 2004 did not explicitly claim responsibility for causing those skeptical of science to use constructivist tactics to diminish the authority of science. Latour also provides examples of critical theorists who he sees as having adopted the positions of conspiracy theorists, such as Baudrillard denying that the Twin Towers fell because of a terrorist attack (Latour, 2004, p. 228). According to Latour, "conspiracy theories are an absurd deformation of our own arguments, but, like weapons smuggled through a fuzzy border to the wrong party, these are our weapons nonetheless" (2004, p. 230). Taking a weaker reading of this claim than Fuller seems to have done, Latour saw that critique in science studies is of the same species of argumentation or explanation as a conspiracy theory.[8] To combat being "considered as friends by the wrong sort of allies," Latour advocates taking a "stubbornly realist attitude" and deal with "*matters of concern*, not *matters of fact*" (2004, p. 231).

While in 2004, Latour argued that Whitehead's metaphysics could be useful to STS scholars for strengthening their positions against conspiracy theorists, he has more recently

[8] While this is not relevant to my project, I would disagree that there is such a relationship between critical approaches to science and conspiracy theories. Conspiracy theories have the character of being unfalsifiable, involving intentional deception on the part of human actors, and active efforts by those actors to thwart investigation (Keeley, 1999). STS analyses do not need to rely on individual actors to account for a phenomenon, even though individual actors may be involved. Additionally, especially in the case of lab studies, empirical evidence can be introduced to falsify a claim. In STS, the absence of evidence is not further support for a claim, as is the case in a conspiracy theory.

offered an alternative. Specifically, he says that understanding how misinformation arises and takes root would enable scholars to combat purveyors of alternative facts (Kofman, 2018). In Latour's *Down to Earth: Politics in the New Climactic Regime* (*Où atterir? Comment s'orienter en politique*) (2018), he describes the ultimate cause of the dissemination of misinformation as the tension between local and global views of nature and reality. He argues for making global views more immediate in everyday local contexts and, thereby, creating a scaffold for understanding the common large political and environmental threats our shared world faces.

While I agree with Latour's proposed solution to the problem of local experiences of reality being in conflict with global ones, I think there is also a need to understand local experiences on their own terms. I am particularly interested in local views of scientific knowledge, whether it is those of scientific experts or those of the lay public. My project attempts to make sense of how a laboratory of biologists makes sense of their work and the role communication plays in it.

Latour's 2004 reflection on the science wars offers resources to pursue my objective. He distinguishes analyzing a "matter of concern" from a "matter of fact" in two ways. First, he articulates facts as not all that is given in experience; instead, they are partial renderings of matters of concern (2004, p. 232). Facts are naturalizations and objectifications from pursuits of matters of concern. By pursuing an understanding of matters of concern, Latour hopes that critical theorists will develop a new tool of analysis and description. This tool, he hopes, would be to add reality to matters of facts as opposed to subtracting from their reality (2004, p. 232). Second, he appeals to Heidegger to clarify that matters of concern are closer to the totality of things that give rise to them having particular features. For instance, a jug is more than a vessel. It is unique and has qualities that emerge in different contexts and when in relation to other

things. A task for science studies would be to investigate how facts about the natural world emerge through the thing called science. A related Heideggerian concept is his own use of the word "concern." In his account, part of the structure of the beings we are involve concerns that we pursue through projects (Heidegger, 1962).

In this dissertation, I use Latour's concept of pursuing a study of matters of concern to investigate the cares or concerns of Lab X. Since they are concerned with making claims about reality, I take their commitment to reality seriously, as it is necessary for the production of things which one would call facts. In investigating how they carry out their project of making claims about reality, I focus on what makes that process possible. As my work will show, a great deal of the lab members' effort goes into negotiating what counts as real amongst each other and how to communicate this to the rest of their field, while also training their junior members to do the same. My research here reveals the centrality of communication beyond the lab and pedagogy to the lab's project of producing facts. By pursuing their concerns over their communicative and pedagogical efforts, I reveal the obstacles the mundane practices of current biological research pose for their work. I also sketch how the complexity of contemporary biological research demands the majority of Lab X's communicative efforts, leaving little, if any, for communicating the content and significance of their work to the lay public.

The communicative activities that I investigated took place almost entirely in the context of Lab X's twice-a-week lab meetings. However, the epistemic significance of Lab X's communicative practices is not readily conveyed using the categories that the lab members used, which is a departure from ethnomethodologically-oriented works in science studies. This is for two main reasons. The first can be best described as the messy practicalities of communication in this lab. As I will describe in more depth later, these meetings were up to three hours long and

had many functions including: a journal club, work-in-progress updates, data analysis, experimental design, grant writing, practice talks, responding to reviewer comments, and reviewing manuscript drafts. This is all to say, the lab members used this time for high priority items that were essential for keeping the lab funded and their students progressing. They also used these activities as opportunities to train the junior members of the lab. These were high-pressure meetings, many lab members expressed to me, and each other, the most stressful parts of the week were these meetings.[9] Their language was highly technical and lab members frequently were unfamiliar with the objects on which other lab members worked, but were still expected to contribute productively to helping their colleagues on the spot. There were also significant language barriers the lab members had to overcome. While English was the shared language of the lab, there were six other languages that individual members were more comfortable speaking. As a result of these factors, the shared categories that lab members used cooperatively in the context of their collaborative work were both few and often not central to what they saw themselves doing in a given moment.

The second reason why Lab X's own categories did not capture the epistemic richness of their discursive work is because in those moments *they* were concerned with arriving at facts. Whatever their matters of concern were in those moments were not made explicit in their conversations. *My* project is about their matters of concern, which are not the facts they produce, but how they pursue their project of making claims about reality. This necessarily includes concepts and objects which do not appear in their language. Such things include standards, training, subjectivity, objectivity, materiality, normativity, and justification.

[9] One of the lab members was also an anesthesiologist who expressed that keeping people alive in surgery was relaxing in comparison to the lab's meetings.

While STS has not defined what sort of analysis works at this level, the current trend toward investigating practice in the philosophy of science has. Michael Weisberg has deployed the method of "working at the epistemic level of analysis" that involves asking "what categories (or language more generally) does one need to provide philosophically adequate understanding of practice?" (Weisberg, 2012, p. 19). While my project is not within the domain of analytic philosophy, I take a similar approach to analyzing Lab X's matters of concern and how its members pursue them. The categories I deploy are meant to capture what is happening at an epistemic level in the lab members' conversations as it relates to their broader objectives, which are entanglements of pedagogy, some degree of outreach beyond the lab, and knowledge production.

I contend that studying "matters of concern" and working at "the epistemic level of analysis" respond to concerns about studying science in a post-truth political climate. First, by attending to scientists' matters of concern (e.g. justification, explanation, pedagogy, communication to those outside of the lab), an analyst is not in danger of making determinations about correctness of a scientific claim or, as Latour would say, subtracting from its reality. Instead, an analyst with social scientific or philosophical training is focusing on aspects of scientific practice which are relevant to the production of a scientific fact, but not the products of science themselves. Additionally, scientists' matters of concern are generally in the areas of expertise that social scientists or philosophers have. For example, a philosopher would generally be more suited to providing an account of biologists' justificatory or explanatory practices as opposed to, for example, how enzymes activities affect cell division. In the case of a social scientist, they would most likely be more qualified to study the role of social interaction in the production of a scientific explanation than assess the merits of the explanation itself. By studying

matters of concern, an STS scholar concerned with doing critique can investigate a crucial aspect of scientific practice that they are uniquely suited to analyzing.

Working at the epistemic level of analysis provides a framework one can use while pursuing matters of concern. However, it is necessary to ground any categories that an analyst develops in the practice they are studying if they are moving away from relying strictly on the language of practitioners. If the categories are clearly informed by the phenomena of an interaction or the laboratory's epistemic culture, a researcher who has become part of a laboratory can bring their training as a social scientist or philosopher to bear on their empathetic understanding of their lab (Cetina, 2009). In doing so, the analyst carves out their own domain of inquiry that works alongside that of the scientists they are studying that could even be helpful for the scientists' own projects.

1.4 Justification of Approach

My justification for working at the epistemic level of analysis stems from two related bodies of scholarship: ethnomethodology and phenomenology. Specifically, I use the concepts of vulgar competency and empathy as means of describing how the categories I use to describe Lab X's practices are sufficiently justified for pursuing my own project. From ethnomethodology, Lynch supports "tutoring one's audience in the competence systems" of a given site (Lynch, 1997, p. 104). A prerequisite for this is that one, the ethnomethodologist or analyst, understand the competence systems present in a particular interaction. To have a "vulgar" understanding of a phenomenon or practice is to go beyond having a textbook understanding of, in my case, neurobiology (Lindwall & Lymer, 2005). For Lynch and other ethnomethodologists, one must

know the specific "what" at the core of a given discipline is (Lindwall & Lymer, 2005; Lynch 1997).[10] By understanding not just the area in which Lab X worked, but how a member of the profession works in that area, I attained an adequate competency regarding the phenomena I describe and analyze in the subsequent chapters.

While my analysis is not dependent on the categories the members of Lab X deploy in their ordinary lab meetings, it is dependent upon the phenomena I observed and recorded. As Garfinkel and Wieder prescribe, I recognize, identify, and follow the development of order in local production" (Garfinkel & Wieder, 1992, p. 182). Furthermore, my commitment to the "real worldliness" of the phenomena in these lab meetings means that the phenomena shape how I investigate them (Hester & Francis, 2000). This is not to say that my research here is objective in a "view from nowhere" sense. My project is certainly from a perspective; however it is one that is informed by an adequate understanding of Lab X's kind of research within neurobiology and the everydayness of the profession.

I draw on the phenomenological concept of "empathy" and, in particular, Alfred Schutz's implicit use of it. In phenomenology, empathy is a technical term. "In empathy the empathizing I experiences the inner life or, to be more precise, the consciousness of the other I" (Husserl, 2006, p. 83). It is a kind of perception which discloses another individual as a subject. Schutz offers an applied version of this concept in his *Phenomenology of the Social World* when he describes how another subject is disclosed as another "I" in experience – their "lived Body is present to me in its fullness of indications *as a field of expression* for their subjective experiences" (Schutz, 1967, p. 163). Schutz clarifies that one does not experience another's experience as one's own. Instead, it as well as the other subject's consciousness appears through their lived body and its activities.

[10] This has been formulated as Garfinkel & Wieder's unique adequacy requirement.

This reciprocal awareness of two subjects as subjects enables them to participate in an activity together and have an awareness of each other's understanding of it. This is partially revealed through mutual coordination of talk and action, as well as the mutual experience of having shared something (Schutz, 1967, p. 164).

In the context of my time in Lab X, I was there for three years as a researcher and was accepted as a member of the lab. I participated in their lab meetings, helping with grant-writing, offering feedback on responses to referee reports, and discussing experimental design in meetings. I was not a fly on the wall, but an intentional participant in the unfolding actions of the lab meetings. The members got to know me and I got to know them. They knew when I did not understand something or felt like I could contribute something meaningful. I also knew when they were understanding what was under discussion or something I had said. I also knew when they were struggling to grasp something or express something or maintain confidence in themselves. In a very ordinary sense, we shared experiences of each other as social beings in a professional setting and as beings who were performing intellectual and communicative tasks.

My presence in Lab X as an informed participant enabled me to attain a kind of "empathetic validity" with the members of my site. By this I mean that the mutual empathetic perception we had of each other that developed over years gave me insight into what the goals were of particular interactions in the lab. I did not attain this kind of "validity" for everything I observed or recorded. Because of that, I have limited this project to that for which I did attain this kind of empathetic validity.

1.5 Lab X

While most of this project is concerned with the specifics of Lab X, I want to provide an overview of when I got into the lab and of the lab members' research. In late August of 2014, I started attending meetings with Lab X, a neurobiology lab in the school of medicine and neuroscience academic unit at a leading research university. The lab is primarily concerned with age-related neurodegeneration in conditions such as Alzheimer's disease (AD) as well as Down Syndrome (DS), Huntington's disease, and Parkinson's disease. The lab does their work on the level of cellular and molecular biology; however, it also makes forays into systems biology, and also sometimes employ behavioral methods more characteristic of psychology. The lab conducts biomedical research at the cellular and molecular level of these neurodegenerative conditions; however, the majority of its work has been on DS. Lab X aims to explain the cognitive aspects of DS by investigating its genetic underpinnings.

The work that the lab does focuses on the neurobiology of neurotrophic factors, actions, and signaling. Neurotrophic factors are proteins which influence the developing brain (e.g. neuron specification or "cell fate," call body migration, axon pathfinding, synaptogenesis, etc.). Their hypothesis is that the neuronal dysfunction and degeneration that occurs in age-related disorders results in cognitive deficits. More specifically, dysfunctional intra-cellular signaling mechanisms are hypothesized to result in the overexpression of certain proteins (amyloid precursor protein (APP) and its substrate amyloid beta (Aβ)), and these in turn are hypothesized to be responsible for cognitive effects of diseases such as AD. The lab's primary focus is on APP's involvement in neurodegeneration. APP is a highly conserved protein, which means that it is present in many organisms and has been maintained by evolution despite speciation. As a result, it is possible to study APP in non-human organisms, including Lab X's choice model organism, *mus musculus*, also known as "the mouse." The mice that they use have been

genetically modified to have a duplication of the mouse equivalent of human chromosome 21, and so they can serve as "Down Syndrome mice."

The overall study involved twenty-two participants but focuses most significantly on about 10 of them. In addition to conducting audio recordings of lab meetings, I also collected data through direct observation, participation in lab meetings, interviews, taking field notes, and analyzing documents including grant proposals, reviewer comments, research articles, and laboratory manuals. The overall period of formal research was for one year preceded and followed by a total of two years of informal research. On average, I spent about six hours a week with the lab members in their meetings with occasional walks with them around campus or at various talks.

Chapter 2

A Brief and Shining Moment: Biology as Humanism at the Salk Institute (1968–1972)

2.1 Introduction

Questions regarding what approach STS ought to take to studying science in the so-called "post-truth"[11] era emerged in 2016, the last year in which I was in Lab X. By 2017, I attended the lab meetings rarely, but enough so that I was aware of the members' anger about restrictions on immigration and the rollback of environmental protections. Outside of the lab, I had become aware of the concerns in STS about the status of scientific facts and the problems this posed to critical studies of science. If one of the intents of STS is to reflect critically on the authority of science, could it be destructive to do so in a time in which there is a perception that institutions of scientific knowledge production are no longer the main determiners of facts about the world?[12] Whether the current debates in STS described in the introductory chapter result in something akin to the science wars of the 1990s remains to be seen. However, the current

[11] "Post-truth" was the Oxford English Dictionary's word of the year in 2016. Casper Grathwohl, the OED's president of dictionaries, reported usage of the word spiked in June 2016 around the time of the Brexit vote and then again once Trump had secured the Republic presidential nomination. Grathwohl traced the usage of "post-truth era" to print and televised news media (Calcutt, 2018).

[12] While it is unlikely that a presidential election gave rise to the concern that the authority of science is under attack, it appears that certainly by March 2017, this concern had grown.

moment in which the category of "fact" has been destabilized in non-academic contexts creates an opportunity to view the history of STS from a critical perspective.[13]

My overarching interest in this project is the communicative methods by which people in their everyday activities try to make determinations about reality and what socio-material conditions make this possible. Upon the emergence of "alternative facts" as a meaningful combination of words in 2017, I returned to the foundational texts of STS to make sense of my own position conducting an ethnography of science.[14] While doing so, I reconsidered how I ought to relate to my site. A natural point of comparison was Bruno Latour and Steve Woolgar's *Laboratory Life* which, as I will describe below (2.2), has parallels to the study I conducted.[15] In this book, the focus is on the everyday life within the lab; however, what is absent is an account of what the lab members themselves thought they were doing and why they thought it was important. Latour's intentional stance of the anthropological stranger afforded him and Woolgar a valuable perspective on the sociality of science. The situation of 2016-2019 with its anxieties about the authority of science have made me wonder what the social and political climate was like when Latour was in his lab at the Salk Institute.[16] More importantly, I found myself asking what the members of his site *thought* about the relationship between their research and the social and political climate of their time. Additionally, I became curious about what had changed in the biological sciences. I also wondered what scientists had changed about their relationship to the

[13] This destabilization can be seen in the increase in number of people who do not have their children vaccinated due to their fear or skepticism of vaccines (Hough-Telford, 2016); the deregulation of environmental protections (which started in 2017); and proposed cuts to the National Science Foundation's budget in 2018.
[14] Kellyanne Conway used this expression in a Meet the Press Interview on January 22, 2017 to defend then White House Press Secretary Sean Spicer's statement about the number of people who attended the presidential inauguration. In this interview, she said that Spicer had provided "alternative facts."
[15] Latour's text was a natural point of comparison for my project because: a) his was the first laboratory study; b) this study occurred less than two miles from my lab; c) he has alternatively championed, reflected upon, and reimagined the function of critique in STS.
[16] The present for this project is 2018-2019.

lay public since the 1970s and if that were relevant to my own site and project. Based on my discussions with the members of Lab X about my work, I also became interested in how Latour's biologists at the Salk saw his work and how Lab X's biologists saw my work. Did they see value in laboratory studies? Did they see a place for social studies of science?

This chapter provides an account of how the founders and earliest scientists of the Salk Institute saw their research relating to the "human affairs" outside of the lab from 1968-1972. Here I focus on the Salk's failed humanistic endeavors which focused on public education and outreach. I contextualize these efforts within the lingering concerns stemming from WWII about the connection between morality and science. I specifically focus on what the founders' motivations were for pursuing a largescale initiative that attempted to establish an interface between the lay public and professional biology (2.3).[17] I use the word "failed" in a very specific way. I mean to use it to assess the Salk Institute's activities by the standards its own members set forth. They intended to transform professional biology into a field that examined and addressed issues pertaining to social issues, ethics, and human nature. The institute founders also sought to establish lasting institutions that would inform the lay public of advances in biological research while ceding authority over the direction of this research to this public. Neither of these things happened in the way that the Salk Institute's founders hoped that they would. By the lights of the standards they set out, these efforts resulted in failure. By *my* lights, these efforts did affect the

[17] By "lay public" I mean to refer to people who are not scientists and are not preparing to become scientists. This is an intentionally broad category. I mean to refer to people who have had minimal science education, or formal education in general, as well as those who have had considerable education, but did not focus on the natural or physical sciences. As you will see, Jonas Salk was concerned with educating the lay public with specific attention to those who were not highly educated. Jacob Bronowski and Charles Percy Snow, on the other hand, were concerned with educating the "non-scientifically literate public," which referred to people who were highly educated, but were non-conversant on topics in the natural or physical sciences. When I use the words "lay public" or "public" and it is in the context of my own argument, I mean to refer to this broad category and not the narrower category with which Bronowski and Snow were originally concerned.

agenda of professional biology through the 1990s and the emphasis on ethics and education are present in everyday biological practice today.

This chapter discusses how these ethical and communicative motivations gave rise to the Council for Biology in Human Affairs (2.4). I show that the prominent scientists, doctors, and other academics across the United States, who comprised this Council, made concerted efforts to incorporate humanistic concerns into the purview of biology as a discipline. The Council was, ultimately, unsuccessful in creating lasting mechanisms within the biological sciences to educate the lay public and involve non-scientists in decisions regarding the direction biological research should take. I will argue that this is because they did not understand the lay public's concerns about science. Despite this failure, this case is useful for seeing how biology, as a set of material techniques and as a profession, has changed since the 1970s. In the concluding section (2.5), I describe how biologists who entered into the profession in the 1980s and 1990s began to face new circumstances that altered the earlier humanistic motivations which drove leading scientists to devote their time to public outreach.

The chapter ends with the questions this historical case brings to the foreground when analyzing biologists' present set of practices and challenges. Summarizing these questions, they are: why aren't there largescale public education initiatives like there were at the Salk Institute? What happened to the emphasis on morality that was present during the decade after the Salk was founded? Where did biologists' focus on communicating the significance their research go? What does it mean to do a lab study now?

2.2 Lab Studies after Latour

Bruno Latour arrived at the Salk Institute in October 1975 and was a presence in Roger Guillemin's neuroendocrinology lab until August 1977. Although Latour's background was in theology[18], he gained experience in anthropology while conducting fieldwork on the Ivory Coast prior to arriving in La Jolla. On a Fulbright Fellowship and a NATO Fellowship, Latour came to the Salk still acquiring fluency in English and unfamiliar with the biological sciences (Latour & Woolgar, 1979, p. 9). This did not deter Latour and he became a part of Guillemin's lab, enjoying "office space, free access to most discussions and to all the archives, papers and other documents of the laboratory, and part-time employment as a technician in the laboratory" (Latour & Woolgar, 1979, p. 39). Following his twenty-one months in the lab, he collaborated with Steve Woolgar to bring together his accumulation of field notes, formal interview records, and the lab's drafts of articles, letters between members, memoranda, and data sheets.[19] The result of Latour and Woolgar's collaboration was *Laboratory Life: The Construction of Scientific Facts*, which stands as one of the most influential texts in Science and Technology Studies. It is one of the earliest works in the tradition of laboratory studies and marked a turning point in science studies toward investigating scientific practices as they unfold in everyday contexts.

Subsequent ethnographers of science have built upon Latour's focus and method for studying sites of knowledge production. Some have approached their sites with great interest in the details of the scientific work in which their participants engage (e.g. Alač, 2011; Lynch, 1997). Other lab studies have investigated the role of social categories in the production of

[18] Latour is a lifelong Catholic and has written about the kind of religious devotion he believes is appropriate. He has argued that religion should not be understood as a set of beliefs (Golinski, 2010). Golinski (2010) has argued that, for Latour, religion was only cast as a set of beliefs in response to the new epistemological primacy of science. While Golinski disagrees with this, he argues that Latour believes prior to the rise of science, Catholicism operates performatively and makes the divine present through the act of enunciation (2010, p. 55).

[19] Latour and Woolgar met in California in 1975 and apparently hit it off. According to a *New York Times Interview*, Woolgar was intrigued by Latour's interest in applying an anthropological approaching to studying a laboratory of scientists (Kofman, 2018).

scientific knowledge (e.g. Helmreich, 2001), compared practices across sites (e.g. Knorr-Cetina, 1981; 1999; Osbeck, Nersessian, Malone, & Newstetter, 2010), or employed ethnographic methods to study knowledge producing practices outside of labs (e.g. Suchman, 2007; Verran, 2001). Others in STS have also challenged the theoretical concepts Latour and Woolgar developed out of *Laboratory Life* including actor-network theory (e.g. Collins & Yearley, 1992) and Latour's intentional stance as a stranger (e.g. Amsterdamska, 1990). There have been some laboratory studies, such as Park Doing's work, that have also made efforts to thematize how the changes in the techniques of biology and its increasing dominance over physics in the 1990s affected how ethnographers relate to the biology labs which they could study (2009).[20] While my project is not comparing the rise of one science and the relative fall of another, it does share a similar interest in how biology changed rapidly in the 1990s and how this affects the position of ethnographers of science.

Doing conducted an ethnographic study of a Cornell "x-ray laboratory," containing physicists and biologists, at which he was employed as a technician prior to his PhD work (2009, p. 39). While he was there as a technician (1991-1999), the "science wars" unfolded. Additionally, biology became increasingly specialized during the Human Genome Project which corresponded with disease-focused biology prioritizing explanations at the genetic level and promoting genetically-standardized models.[21] During Doing's tenure in his lab, he did not

[20] A very clear way in which biology gained dominance over physics was in 1993 when the US Congress officially cancelled the development of the superconducting super collider. The Department of Energy had criticized the project due to its high costs and poor management in a letter to President Clinton (Brian, 1993). 1993 was also the year that the National Human Genome Research Institute published its five-year plan in *Science* and Francis Collins succeeded James Watson as the director of this institute.

[21] Biologists started specializing in increasingly narrow areas of focus. For example, during the Human Genome Project research programs grew up around particular organism and then (circa 2008) particular genetically modified variations of a particular kind of organism. This narrowing of focus happened contemporaneously with the growth of biology as a field. Between 1981 and 1999, the size of research teams in biology increased by 50%. Furthermore, international collaborations in which a team member was at a US university increased five-fold during this same period (Vermeulen, Parker, & Penders, 2013). The more biologists on a particular study enabled team members to

experience the effects the Human Genome Project had on the biological sciences. This is due both to the focus of his lab and to his time in the lab being prior to the fruits of the Human Genome Project percolating into the ordinary practices of non-biomedical and non-genetics labs. This is all to say that while Doing was situated in a biology lab during a significant time for the field as it expanded, fractured into specialized subfields, received massive amounts of funding, and transformed its epistemic standards, he was too close in time to see these changes. Additionally, his position as a technician during the time in which he was acquiring his field data shielded him from the fallout from the science wars.

I have said this to communicate that the standpoint of the present (2019) offers an opportunity to outline some of the consequences of the Human Genome Project and the science wars for both biologists and ethnographers of biology. There is much to be said about the increasingly international and intercultural nature of biological practice, the field's efforts to correct gender imbalances, the development of "biotech" as a distinct field, the relationship between academic and industry labs, biology's recent foray into "big data," and the uses and abuses of labor in biological practices and techniques in the Global South. All of these topics emerged, to some extent, during the course of my time in Lab X. However, my focus in this overall project is on my lab's internal communicative practices with each other and with the lay public. By examining how lab members communicate with each other in the course of their work to understand neurodegenerative conditions, I show core ways in which biological practices have changed since Latour's time at the Salk. Specifically, I show how the 1990s marked a key moment that transformed the focus of practitioners' training and outreach efforts.

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develop a deep expertise on a particular topic because they knew other team members would provide their expertise on other dimensions of the project. In short, generalists became less valuable because the number of practicing biologists increased.

The study that I conducted of Lab X has several similarities to the one Latour conducted of Guillemin's lab at the Salk Institute. For instance, Latour and I studied biologists within the same subfields. However, our experiences also depart in significant ways that speak both to the availability of institutional resources and to biology's relationships to lay audiences that were present during our tenures in our labs. While Lab X, founded in 2009, did not exist during the time of Latour's study, it has since collaborated with scientists at the Salk.[22] Furthermore, the Salk, while contributing to many different areas of research, has shared foci with Lab X including: neuroscience, genetics, aging, and Alzheimer's disease. During the time Latour was present in Guillemin's lab, the Institute, as a whole, was exploring the new field of neurobiology and making advances in "new genetics" research. While neurobiology in the 2010s is different than neurobiology was in the 1970s, the practitioners in both labs and times were focused on diseases and genetic conditions. Specifically, both Lab X and the Salk Institute had interests in conditions that affected either the very young (including the embryonic stage) or those advanced in age.

Like Latour, I was also invited into my lab. Latour had developed a friendship with Guillemin when they met in Dijon, France prior to Latour travelling to the Ivory Coast for his anthropological study (Kofman, 2018, p. 11). This relationship later facilitated Latour's access to the Salk Institute. While I did not have a pre-existing friendship with the director of Lab X (who I call "Lawrence"), he wanted me to participate in the lab. I was introduced to Lawrence by my advisor as someone who had a background in philosophy, specifically on the phenomenological

[22] Lab X and one of the Salk's genetics labs has collaborated on work on mouse models of neurodegenerative disease. Members of the Salk have worked together to put on a conference for the Down Syndrome Affiliates in Action. They have also identified a treatment for a degenerative nerve disease (Charcot-Marie-Tooth Disease). Along with Sanford-Burnham, the Salk and Lab X have also identified how Down Syndrome lowers the level of a particular protein in the brain (sorting nexin 27). One member of Lab X is a former director of a unit within the Salk Institute.

concept of empathy. While Lawrence saw "empathy" as being synonymous with "compassion," which differs from "empathy" in phenomenology, he was intrigued by someone who studied communication. I, and Lawrence, attributed his interest in empathy to his training as a medical doctor. While he completed an MD/PhD in neuroscience, his real interest in research on Down syndrome and Alzheimer's disease emerged because of his clinical work. His interaction with patients, he said, gave rise to his belief that all disease as an issue of communication. In the case of a neural disease, one would call it a disease because the neurons are unable to communicate with each other. In my interactions with him, I gathered that he saw us as working on the same problem of making things better for patients with neurodegenerative conditions, but using different methods. He described my work to the lab members as "synaptogenesis, but between people. She does what we do, but with larger things" (October, 2015).[23] Despite the differences in our initial understandings of what each other did, Lawrence welcomed me into the lab and valued my presence there.

However, there are some significant differences between Latour's study and my own. Guillemin saw Latour as conducting an anthropological study of the scientists in his lab. On the other hand, Lawrence specifically contrasted my work with Latour's when I introduced my project to Lab X in one of their meetings. "She is really doing *real* sociology of *science*" (September, 2015). While the members of Lab X were largely unfamiliar with STS and philosophy of science, the senior scientists were somewhat familiar with *Laboratory Life* and Latour's study. Many of them had friends at, and collaborated with members of, the Salk Institute and they told me that Latour's two-year stay there occasionally came up in

[23] Synaptogenesis is the formation of synapses between neurons. A synapse is a structure that allows a neuron to pass an electrical or chemical signal to another neuron or target cell.

conversation. The key difference Lawrence saw between my project and Latour's was that I studied *science*, albeit from a social perspective, whereas Latour studied *scientists*.

Despite Lawrence's warm and supportive welcome, Latour was afforded significantly more access. Guillemin provided Latour an office in the lab as well as part-time employment as a technician, which supplemented the stipends he received from his Fulbright and NATO fellowships. Additionally, he had access to the entirety of the lab's space and all its written materials (Latour & Woolgar, p. 79). While I did acquire grant funding, I was employed as a teaching assistant in Communication for the majority of the time in which I conducted my fieldwork. Furthermore, while I had access to all of the lab's meetings, I did not have access to the entirety of the lab's space nor all of its written materials. I was not allowed in the "T-Room" of the lab's space where almost all of their wet work occurred. This is because one had to have training to be in that room. The training itself was expensive and was carried out by either Lab X's manager ("Lisa") or their "mouse person" ("Monica") as well as a technician outside of the lab. People working in that room also had to complete safety training courses for which Lab X paid. Expenses accumulated due to: the time Monica or Lisa had to devote to this training, the compensation the outside technician received, and the materials used in this training. The lab had to spend these resources to train every new member because, once a year, the University conducted a health and safety inspection. The lab also received inspections to ensure they were meeting NIH guidelines for working with experimental animals. Because of the cost of allowing a single person into the T-Room, it was a waste of funding to pay for me to be in that room simply to observe. Furthermore, the risk of contamination was always a concern and allowing yet another person in the room increased that risk. Regarding the written materials, the lab did not have a central location for all of the documentation it produced. Whereas Guillemin's lab used

physical papers, Lab X worked almost entirely with digital documents that were stored (or not) by one or more members. Asking a lab member for a draft of a grant created a not insignificant amount of labor for them as they hunted through their computer and emails to uncover, or to figure out who might have had, the draft I was requesting. Because I was dependent upon the goodwill of the lab members, I did not push to get many documents and certainly not if they expressed any concern amongst themselves about the information circulating outside of the lab.

Other differences in our experiences were the ways in which the members of our sites perceived the potential utility of our projects. The members of my site saw my work as, ideally, being helpful for *them* communicating what they were doing amongst themselves as well as to the public. However, many expressed doubts regarding the possibility of public outreach. "Sai," a senior scientist, expressed doubt by saying, "How can I explain what I do to a lay audience? I am looking at gene expression dysregulation in fibroblasts by analyzing RNAseq data. That doesn't make sense to anyone" (September, 2015). Instead, the lab members stated that it was more pressing to improve communication across the subgroups within Lab X, to other labs, and other biologists outside of their immediate subfields. I helped on these fronts in two main ways. One of the roles I played during meetings in which lab members strategized about how to respond to reviewer comments on a paper or a grant was that of a somewhat-informed outsider who had objections. In these discussions, lab members would ask me to come up with arguments against their findings or their proposed projects.[24] In related meetings during which they would finalize papers before submitting, or resubmitting, them to journals, I would be asked to assess the "logic" of the argument.

[24] For example, on one occasion when they were planning to submit a grant to test a vaccine that would determine the effects of gamma-secretase modulators in Down syndrome mice. They asked me to come up with a challenge to the proposal and I asked what their rationale was for not using an additional mouse line.

Another function I performed in lab meetings was to help lab members understand each other. As one of the three native English speakers who consistently showed up to lab meetings, I was able to facilitate communication between lab members who had different native languages. For example, one meeting occurred shortly before Halloween in 2016 and a project scientist ("Pei"), whose first language was Mandarin, asked a graduate student ("Josefina") what her plans were for the "holiday." Josefina's first language was Spanish, and she was unable to understand Pei's question. After struggling to understand one other for a bit, I supplied the word "Halloween" to Josefina, which allowed her to understand the point of Pei's question. In the context of the lab members' discussions of biological research, I was occasionally unsure of which particular protein or gene a particular member was speaking about, especially, if it was not one with which the lab usually dealt. In these cases, I would try to communicate phonetically what one lab member was saying to another member.

For example, in the preliminary phases of designing a study to complement a collaborative project with the Salk, Pei proposed using mice that Lab X did not normally use. He suggested that they compare the results of his proposed experiment between two lines of mice. Specifically, the mice he wanted to use were two kinds of "Gars" mice.

"We can compare between Gars +/+ and Gars ^{P234KY}," Pei said, with the "r"s in "Gars" sounding like an "l" and without an "s" on the end. Pei's "w"s also sounded similar to how he used the "v" sound. Because of this, it sounded closer to "Gall-plusplus and Gall-P tventy-three four kai."

Pei was trying to communicate this to "Hana," a postdoctoral student whose first language was Japanese. Both Pei and Hana had learned English in environments that focused on written English and they had little experience with conversational English prior to joining Lab X. In response to Pei, Hana said,

"Gall? What is Gall?"

After Josefina was unable to offer a clarification and Lawrence had not weighed in, I said,

"Gar plus plus? And Gar twenty-three for Kai?"

"Oh! The Gars mice – 234KY" Josefina exclaimed at the same time Hana said, "Oh, those mice!"

While I generally understood the phonetics of what Pei was saying, I misunderstood the meaning of his statement. I roughly facilitated the right sounds and only by virtue of the shared background knowledge of the other lab members was I able to facilitate Pei's intended meaning. This was ultimately a problem of me not having the disciplinary background which would have enabled me to recognize that he was referring to a certain mouse line the lab did not normally use. For the first mouse I captured the relevant fact that it was a +/+ mouse, but I had missed the "s" in "Gars." However, in the case of the second mouse, I misunderstood that the list of numbers was specifying a particular kind of Gars mouse and not saying what it was a model of. I had thought that the mouse line was called "Gar 23" and it was a model *for* a Kai gene. However, my attempt to communicate the sounds of what Pei had been saying in my Californian accent enabled Josefina and Hana to identify to which mouse line Pei was referring.

It is unclear from Latour's account how he contributed to Guillemin's neuroendocrinology lab. However, Jonas Salk provides his perception of the utility of Latour and Woolgar's laboratory study in the introduction to the second edition of *Laboratory Life*. Overall, Salk's account of the book is quite complimentary. Salk thought that the book was not abstract or overly concerned with well-known historical events.[25] He saw other sociological or philosophical

[25] He does not name any.

approaches to science as having no relation to what happens in actual laboratories. Salk described Latour and Woolgar's book as a remedy to these other kinds of approaches to studying science (1979, p. 11). Salk did not see the book as overly concerned with humanizing scientists, telling embarrassing stories, providing gossip, or psychologizing the lab members as science journalists or some social studies of science tended to do (1971, p. 12). Salk found the authors' methods,

> "crude and qualitative, but their will to understand scientific work is consistent with the scientific ethos… For me the most interesting part of the work and its outcome, is that Bruno Latour, a philosopher-sociologist, began a sociological study of biology and along the way came to see sociology *biologically*… Here are sociologists coming to recognize that their work is only a subset of our own kind of scientific activity, which in turn is only a subset of life in the process of organization" (1971, p. 12-13).

Salk's last sentence here is notable. In my interpretation, he is saying that biology and sociology are pursuing the same goal of understanding life. Sociology is either a more specific kind of biology or is covering only a portion of what biology addresses in its inquiries. For Salk, it appears that both sociology and biology are a fundamental kind of activity that humans do.[26]

While it is questionable whether Latour or Woolgar would claim that they came away from the project seeing sociology from a biological perspective, Salk's assessment is compelling.[27] For Salk, Latour's project fit alongside the activities of the Institute members. Furthermore, he did not see sociological work as being inferior to biology, but one of its subsets. He explicitly states that "the final point [of the previous passage, intended to suggest that this book is not unworthy of the attention of scientists], is in the bridge made between science or

[26] To me, this echoes Bronowski's thesis in *Science and Human Values* which is that art and science have the same goal of understanding human nature.
[27] I am unable to come up with a reason to give Salk's statement about Latour's sociological work on Guillemin's lab *less* weight than I would give Latour and Woolgar's statements about the role of credit and the sociality of discovery at the Salk.

scientists and the rest of society" (1979, p. 13). Despite his objection to the authors' accounts simplifying the details of scientific work to make their claim that human affairs are the same as scientific production, ultimately Salk found great value in Latour and Woolgar's project.

> "I am now convinced that this kind of direct examination of scientists at work should be extended and should be encouraged by scientists themselves in our own best interest, and in the best interest of society. Science, in general, generates too much hope and too much fear, and the history of the relationship between scientists and nonscientists is fraught with passions, sudden bursts of enthusiasm, and equally sudden fits of panic. If the public could be helped to understand how scientific knowledge is generated and could understand it is comprehensible and no more extraordinary than any other field of endeavor, they would not expect more of scientists than they are capable of delivering, nor would they fear scientists as much as they do. This would clarify not only the social position of scientists in society, but also the public understanding of the substance of science, of scientific pursuits and of the creation of scientific knowledge" (1979, p. 13).

Jonas Salk saw that the core contribution of laboratory studies was their capacity for communicating science to the lay public. On the one hand, works such as Latour and Woolgar's could demystify what the production of scientific knowledge actually is while humanizing those who generate it. On the other hand, Salk saw studies such as these as having the ability to teach the substance of science to general audiences. He concludes his introduction by predicting that in-house sociologists and philosophers will become common in laboratories and that he has hopes that scientists will be collaborators on future lab studies.

Upon reading Salk's introduction to *Laboratory Life*, one could focus on the question of whether he understood the project undertaken in this text. One could also dismiss his statements as that of someone who was not well-versed in the sociology of scientific knowledge. I am not going to do that. It is noteworthy that Jonas Salk, the developer of the first successful polio vaccine, the celebrity scientist, the figurehead of the Salk Institute for Biological Studies, apparently cared deeply about the lay public's understanding and perceptions of science. Salk's commitment to making biological research intelligible to the public was not something separate

from the aims of the Salk Institute, nor was he the only one to whom this was important. In fact, this commitment to build bridges between laboratories and, as he put it, "human affairs" was a foundational tenet of his institute.

Because my interest is in how biologists' communicative practices changed since the 1970s, I researched the Salk Institute's attempts to build bridges with the lay public. I focused on its members' attempts at public outreach and education during the decade in which Latour spent two years in Guillemin's lab. By the time that Latour arrived, the largescale humanistic endeavors at the Salk had failed. The Fellow dedicated to organizing the various commissions responsible for working at the intersection between biological research and social issues had died one year before Latour arrived in La Jolla. The president of the Salk Institute who provided the organizational and administrative support that enabled the Salk scientists and their colleagues at other institutions to do this work had resigned his post in 1972. However, the echoes of the Salk's educational and humanistic efforts lingered because the scientists who engaged in those attempts continued on in the Institute's laboratories. Yet, these echoes did not translate into additional largescale efforts to educate the lay public.

One scientist who was there through the Institute's failed attempts to bridge the gap in understanding between professional biologists and the lay public was Suzanne Bourgeois, one of the first junior faculty the Salk Institute hired. The historical research I conducted makes use of the account she wrote of the founding of the Salk Institute: *The Genesis of the Salk Institute: The Epic of its Founders*, which she dedicated "to the Salk Institute Founders, Dreamers of the Greatest Generation" (2013). In the forward that Guillemin wrote for this book, he corroborates Bourgeois's account saying,

> "…what this book by Suzanne Bourgeois accomplishes, is to recount the extraordinary story of the ups and downs of each of these moves and the

> personalities involved where, as Harriet Beecher Stowe put it, "every man had his own quirks and twists," to bring us eventually to the Salk Institute.... She personally knew all the characters involved in the odyssey that culminated in the Salk Institute for Biological Studies as we know it today. Personal relationships have been put aside; this book is strictly factual, based on archives, the author's diary, and probing interviews" (2013, p. x).

For Bourgeois, this book was "a labor of love" and a "personal account" that she undertook on her own after she retired. It is based in archival work, her diary entries, and interviews she conducted with her colleagues (2013, p. x). She also acknowledges that she may be biased because she knew all of the "characters" in the book and was friends with many of them, one of whom was a founder of the Institute and her husband of 50 years, Melvin Cohn. Because of the personal nature of this book, I take it as a primary text. I also take the published writings of Jacob Bronowski, a founding Fellow, as a primary text. The bulk of my research, however, is based on the archival work I did in the Mandeville Special Collections on the Jonas Salk Papers. The history I present below is an intellectual one that does not attempt to portray the Salk Institute's humanistic initiatives as successes, as does Bourgeois and the biographer and MD, Charlotte Jacobs. Instead, I provide a historical account of the members' drive to communicate the significance of biological research to the public. I reveal the obstacles, some of their own making, they faced when trying to do so. Ultimately, the members were not successful. However, by following the members' own private records, office correspondences, drafts of grants and mission statements, and published writing, I show the challenges that biologists of the 1970s faced when trying to work at the intersection of biological research and lay audiences' concerns about science and society. What I find striking is that their writings reveal deep concern with the education of the lay public despite the pressing demands of daily life at a new institute. These challenges were serious and ranged from a decade-long struggle to acquire consistent funding to their own lack of experience communicating the significance of their research to a lay

audience. By describing how the members of the Institute tried but did not succeed in establishing an enduring institution of science outreach, it is possible to see how it is even more difficult for contemporary biologists to communicate science to the lay public.

I want to note a final difference between my project and Latour's before continuing on to describe the humanistic endeavors the Salk Institute undertook between 1968 to 1972. Latour's study dug into the everyday life of a laboratory. He described the procedures by which things he called facts were produced and what was meaningful for those acts of creation. It is unlikely that the scientists he studied would call the results they put in grant proposals or sent off to journals "facts." In my time in Lab X, the lab members never once used the word "fact." That is a bold word that has a finality to it. It is a final statement about how some part of the world really is. This is not to say that what Guillemin's lab produced were not significant results. However, for Lab X and most likely the scientists Latour studied, a fact is something that is confirmed and distilled over time. My approach differs from Latour's because it is closer to Ludwik Fleck's (1935) method of providing an account of scientific work. For Fleck, facts crystalize over generations of practitioners working to define and solve a particular problem. My work here is not providing a Fleckian genealogy of a particular fact; however, it *is* moving away from Latour's rigid localist stance toward scientific activity. By letting the past communicative activities of the Salk Institute and those of Lab X reciprocally illuminate each other, I am able to clarify *matters of concern* in professional biology that its members are pursuing on their way to producing *matters of fact*.

2.3 Biology as a Cultural Force

Jonas Salk was motivated from childhood to alleviate the suffering that disease caused, and this continued to be a driving force throughout his career. Ultimately, this pushed him to develop the first safe and effective polio vaccine while also ostracizing him from the medical and scientific communities because of his desire to educate the lay public. Charlotte Jacobs, a professor of medicine and biographer, describes Salk as being deeply affected by witnessing the effects of a terrible flu on New York. He saw horse-drawn carts piled with coffins, children in leg braces, and amputees. According to Jacobs, his home-life and growing up in a Jewish community in the Bronx during the Great Depression made him feel an obligation to "repair the world" (Jacobs, 2015, p. 15). His path into the medical profession was difficult, in part, due to the limited number of offers medical schools made to Jewish applicants. What set him apart, however, was his conviction that he wanted to bring science into medicine (Jacobs, 2015, p. 22). Salk's concern for public wellbeing took precedent over prestigious or lucrative positions. After the attack on Pearl Harbor, Salk immediately abandoned his well-respected internship to work on an influenza vaccine, writing to the director of the Commission on Influenza that he felt his greatest contribution would be working "in a field that has such special implications and significance in war time" (Salk to Thomas Francis, Jr., December 11, 1941).[28] With that letter, Salk packed up his family and moved from New York to the University of Michigan.

Salk's desire to do medical research that could directly impact the everyday wellbeing of all people was the impetus for his work on poliomyelitis. He attracted the attention of Harry Weaver, the director of the National Foundation for Infantile Paralysis (now called March of Dimes). Salk's reputation grew amongst the leaders of the Foundation because of his ability to communicate with the public and get them to understand the scientific work he, and other

[28] *See* Jacobs, 2015, p. 35.

scientists, did (Jacobs, 2015, p.64). However, his interest and success in educating the public marked the beginning of the erosion his legitimacy amongst scientists. By the time Salk had moved to the University of Pittsburgh and was working in earnest on his polio vaccine, the media and the public had already grown accustomed to seeing him as a public figure. Despite his discomfort with his growing celebrity, he insisted that he and his secretary respond to each letter from the public (Jacobs, 2015, p. 104).[29]

Salk further alienated the scientific community while simultaneously keeping the public apprised of the progress of the human trials by going on a special broadcast on CBS titled *The Scientist Speaks for Himself*. The optimism he expressed over the early results from the trial soured the scientific community against Salk because they had not yet had the chance to review his results (Jacobs, 2015, p. 125). However, his appearance on national television gave the Foundation a publicity boost that galvanized the lay public to participate in, what Jacobs calls, "the world's largest clinical trial" (2015, p. 149).

What was significant about the Foundation's polio vaccine trials was it run and financed by volunteers. Furthermore, it was conducted on 2 million children around the United States. Three inoculations preceded by an initial blood draw, one following the vaccinations, and one six months afterwards. Three thousand chapters of the National Foundation for Infant Paralysis responded to the board's call for volunteers as did other organizations. However, the largest percentage of volunteers were self-described housewives. The Foundation coordinated the training of: "20,000 physicians and public health officials, 40,000 nurses, 14,000 elementary school principals, 50,000 teachers, and 220,000 volunteers" (Jacobs, 2015, p. 152). The training

[29] His responses to these letters were notably compassionate and respectful. To a woman who thought cats were responsible for polio, he responded, "It is very kind of you to share this idea with me" (to "Mrs. Robinette," January 31, 1951).

of the volunteers took place over two-day workshops at 211 sites across the country. Throughout the training and the trial, the media depicted the efforts as a national movement against a terrifying disease. The lay public held up Salk as the symbol for the fight against polio, much to his chagrin.

I will not go into the announcement of the vaccine's success, the scientific community's displeasure with Salk's expanding celebrity, and the difficulties he faced winning the approval of other scientists even after he established the Salk Institute. These are all important events, but they are not central to the point I want to make. What I have aimed to communicate so far in this section is that Salk's concern with the lay public's understanding of scientific, and in particular biomedical, research pre-dated his efforts in developing the polio vaccine. In fact, one could argue that his motivation to research and development a vaccine against the disease had its roots in his respect for those outside of the scientific community. To me, Salk most clearly demonstrated his respect for the lay public when a journalist "asked who owned the patent on the vaccine" and Salk answered "Well, the people, I would say. There is no patent. Could you patent the sun?" (*See it Now*, CBS, April, 12, 1955).[30]

The broader point I want to make is that there was a feeling in professional biology during and certainly after WWII that educating the lay public on scientific advances was an imperative. There was also a feeling in this particular scientific community that there was already a gap between the scientific literacy of professional scientists and that of non-scientists. While it would appear that many of Salk's contemporaries were disdainful of public outreach, others shared Salk's desire to educate the lay public.

[30] Reported by Jacobs (2015, p. 174).

By 1960, it had been five years since Jonas Salk had created a "safe, effective, and potent" vaccine against poliomyelitis (polio).[31] Salk had been in talks with his colleagues at the University of Pittsburgh since 1957 about the possibility of starting a research institute that would work at the edge of experimental medicine to apply new biological research in the treatment of disease. However, where and in what form the institute would be established was in flux for a number of years. After a series of false starts to establish an institute at the University of Pittsburgh, Salk collaborated with the March of Dimes president, Basil O'Connor, to refocus the effort. O'Connor both secured the funding and possible locations for the proposed institute, finally settling on a spot on the Torrey Pines Mesa in La Jolla.

O'Connor accompanied Salk to several meetings with potential future members of what would be called the "The Salk Institute for Biological Studies." Two of these potential members were Jacob Bronowski and Charles Percy Snow. It was his interactions with Bronowski and Snow in London that prompted Salk to build programs that bridged the gap between scientists and the lay public into the Institute's plan.

In July 1960, Salk and O'Connor met with Francis Crick. The day after, they met with Bronowski for lunch as well as Snow. In 1959, Salk had read and resonated with Snow's lecture "The Two Cultures," which articulated his perception of the gap between the scientific and non-scientific communities. Salk's time in London helped shape his vision for the institute. In his meeting with Bronowski, they discussed Snow's "The Two Cultures and the Scientific Revolution" lecture which he had delivered at Cambridge (Bourgeois, 2013, p. 97; Jacobs, 2015, p. 240).

[31] Said on April 12, 1955 by Dr. Thomas Francis Jr., director of the Poliomyelitis Vaccine Evaluation Center at the University of Michigan School of Public Health.

The two cultures to which Snow referred were those of the scientist and the educated, but scientifically illiterate, public. Snow and Bronowski resided in both cultures, which made them sensitive to the gap between these two groups. Snow, in addition to studying chemistry and physics, was a popular novelist. Bronowski was a mathematician and had worked for the United King's Department of Home Security developing approaches to calculate bombing efficiency in World War II. He also wrote poetry and books which explained science to the public. He also became a famous television personality appearing on the popular British *The Brains Trust* on which he discussed questions viewers sent in.

By the time that Bronowski met Salk, he had been considering making a career change and saw the appeal of playing an administrative role at Salk's proposed institute. Bronowski saw it as an opportunity to do work to bridge the gap between scientists and the educated, but non-scientifically literate, public, as well as to pursue his creative interests. It was two years before the construction of the Salk Institute was fully underway with the groundbreaking on February 28, 1962. Despite the delays, Bronowski remained committed to joining the Salk and took up the mantel of "in-house humanist" (Bourgeois, 2013, p. 162; Jacobs, 2015, p. 335). From the time he joined the Salk Institute as a founding fellow until his death in 1974, he spearheaded all of the Institute's efforts to develop means of communicating science to the lay public. He also forged connections between his biologist colleagues and those in the humanities and social sciences who were interested in the natural sciences. He invited the Russian linguist Roman Jakobson to stay as a visitor the Salk Institute in 1966 after they had corresponded over the previous two years. At the Salk, Jakobson put on several seminars which increased the Salk Fellows' interest in possible connections between biology and linguistics. With Bronowski's guidance, they invited another linguist, Eric Lenneberg, to give a lecture on "The Biology of Language

Development" in their winter colloquium in 1967. Bronowski continued to facilitate the relationships the Salk biologists had cultivated with linguists by putting on a well-attended meeting on "The Biological Foundations of Language" in 1969. The connections Bronowski established with linguists piqued the interest of junior faculty members, such as Ursula Bellugi, who became interested in children's language acquisition, subsequently founding the Laboratory for Language Studies, which survives now as the Laboratory for Cognitive Neuroscience.[32]

In addition to attracting linguists to the Salk Institute, Bronowski also invited the philosopher of science Karl Popper, who spent two months at the institute. While Popper was at the Salk, he developed friendships with Jacque Monod and Melvin Cohn that led to Monod writing the preface to the French translation of Popper's *Logic of the Scientific Discovery*. Cohn's friendship with Popper and their conversations served as the basis for a lecture Cohn delivered to the *Society for Scientific Temper*.

Contemporaneously with these activities, Bronowski developed a mission statement for the Salk Institute's humanistic efforts. While various versions of the document circulated in the years after the founding of the Institute, Bronowski presented this mission statement to the Fellows, with input from Salk, in 1969, entitling it "Biology in Human Affairs at the Salk Institute."[33] Not simply a statement of the Institute's humanistic mission, Bronowksi, with his flair for showmanship, presented it as a manifesto outlining biology's capacity to speak to humanity's central issues. In subsequent years, the manifesto was rewritten and included in

[32] Notably, she also demonstrated that ASL is a language

[33] Salk's input appears to have been minimal. Bronowski delivered drafts of this statement to Salk since 1968. Salk's comments were generally in the form of marginal comments or notes to his secretary, Lorraine Friedman, asking for clarification or to meet with Bronowski to get clarification. It does not seem that Salk significantly changed Bronowski's thinking. Both Bourgeois and Jacobs report that Salk was very impressed with Snow's "Two Cultures" lecture and Bronowski's statement echoed it. However, Bronowski moved beyond Snow's more general description of the "scientific community" and non-scientists. Bronowski specified that biology was unique in its ability to address issues that were of traditional concern to scientists as well as answer the moral questions of the lay public (including non-scientifically literate academics).

application for an education and public programs grant from the NEH that would fund the hiring for appointments in the humanities at the Salk Institute from July 1, 1970 to July 1, 1974. Excerpts from "Biology in Human Affairs at the Salk Institute" also appeared in many of the Salk Institute's funding proposals submitted to the NSF, the NEH, and the Russell Sage Foundation. Members of the Salk Institute also used portions of this document in their outreach efforts through *Time* magazine. One of the Salk Institute's presidents, Joseph Slater, also used it in his development of the Aspen Institute's description of its own mission regarding communicating scientific research.

In this document, Bronowski begins by sketching the "humanistic import of modern biology." Bronowski claims that the advances in biology make it comparable with the physical sciences, at least with respect to the knowledge they are able to attain. However, biology, unlike physics, provides humans with the opportunity to *control* "the human condition" (Bio. Hum. Affairs, 1969, p. 1)[34]. While the current goals of the biological sciences are to improve the quality of human life, Bronowski predicts that the field's rapid acceleration will cause practitioners to begin to examine the meaning of life itself. In the field's quest to improve quality of life, researchers are already contemplating the values that people hold and how to study them from a scientific perspective. Bronowski argues that the challenges biology faces are increasingly humanistic ones that require collaborations between biologists and humanists. These "humanists" appeared to be philosophers and some variety of social scientists.[35] Interestingly, Bronowski did not express interest in hiring historians as faculty at the Salk Institute in his grant proposal to the Russell Sage Foundation. This was the one place where he, and the other members of the Salk Institute, tried to permanently integrate non-biologists into the faculty. This

[34] Abbreviation of "Biology in Human Affairs."
[35] I will say more about what Bronowski seemed to think about social scientists in 2.6.

is puzzling because Bronowski's own work can be read as intellectual histories, especially his *The Ascent of Man* book and television series (1973). Additionally, in his writings, Bronowski clearly demonstrates that he is aware of the history of science. This omission in the grant proposal is significant because it shows that Bronowski may not have seen how historians could have been useful collaborators. It is an open question, therefore, whether Bronowski saw his own intellectual histories meeting the aims of the Council if he saw those of historians as falling short.

Bronowski continues by describing how the Salk Institute is uniquely positioned to take on this work because it has been doing research to further human welfare. This, he argues, was an implicit motivation for founding the Institute and is born out in the Fellows' concerns about the responsible application of their research (Bio. Hum. Affairs, 1969, p. 2). He further contends that biological, especially biomedical, inquiry investigates what makes humans physiologically unique and motivates researchers to ask what makes humans unique as value-holding beings. Bronowski claims that the vast intellectual scope of biology has inspired the researchers at the Salk to develop a humanistic program. This program would investigate multiple dimensions of the interrelation of the scientific and humanistic such as: biology and a human ethic; biology, the individual and society; and biology and the public. Most of the Salk Institute's humanistic efforts went into the last item, i.e. "biology and the public," which were carried out by the Council for Biology in Human Affairs (the Council), to which Joseph Slater appointed Bronowski as director.

The Council expressed Bronowski's conviction that biology had the unique capacity to empirically investigate the material and non-material basis of human nature. Furthermore, he saw biology as the sole science that had the ability to *alter* human nature and the destiny of

humankind. While a radical position, I would trace it to a shared priority Bronowski and the other founders of the institute gave to the ethical value of their work. This shared priority Bourgeois, Jacobs, and I would attribute to the founders' experiences in World War II. Their experiences during the war made them question the morality of scientific endeavors. The Salk Institute's founders, trustees, and advisors had their careers and perspectives on science shaped by what they had witnessed or done during the war. When they returned home, these men turned away from their previous pursuits in physics, mathematics, or traditional science and became biologists or humanists. Below, I will briefly sketch the career trajectories of some of the founders and what they did in WWII.

Renato Dulbecco was an Italian physician who was drafted into military service as a doctor and was injured on the front lines. After recovering in France, he joined the French resistance of the German occupation. After WWII, he moved to the US. There he became one of the scientists who initiated the earliest preparations for the Human Genome Project in 1986 (Dulbecco, 1986). Melvin Cohn was an American drafted into military service after studying physics and chemistry. During WWII he worked in a medical research team in the Pacific Theater. After the war ended, he, like Bronowski, was deployed to Japan to study the effects of the atomic bombs. During this time, he also treated patients suffering from diphtheria associated with the conditions in which survivors were forced to live (Robbins, 2018). Warren Weaver was an American mathematician who headed the Applied Mathematics Panel in the Office of Scientific Research and Development during WWII. After the war, he became deeply committed to improving public understandings of science. In 1954 he served as president of the American Association for the Advancement of Science and, thereafter, won numerous awards for his public outreach efforts.

Leo Szilard was an Austro-Hungarian born physicist who both conceived of the nuclear chain reaction (1933) and patented the idea of a nuclear reactor (1934). He wrote the "Einstein-Szilárd letter" which outlined the possibility of creating a chain reaction in uranium, which would generate large amounts of power. This letter cautioned that this technology would lead to the development of dangerous bombs. This letter led President Roosevelt to create the Advisory Committee on Uranium, which began the US's work to develop an atomic bomb. A month before the bombs were dropped, Szilard wrote a petition, signed by 70 scientists working on the Manhattan project, in which he argued that the bomb should not be used on a civilian population. In 1946 Szilard transitioned into biology after the regret he felt over his role in the development of the bomb (Coffin, 1964, p. 1). In addition to his work at the Salk Institute, he grappled with his feelings of guilt through short stories. In 1961, he wrote *The Voice of the Dolphins* in which he reflected on the moral issues raised by the Cold War and his own perceived role in its inception.

Edwin Lennox was a physicist and the son of Jewish immigrants. WWII interrupted his graduate work and he accepted a job in Los Alamos, New Mexico to work on the atomic bomb. Lennox was present during the testing of the first bomb. Jacque Monod was a French biochemist and became the Chief of Staff of Operations for the French Forces of the Interior in WWII during which he organized resistance activity. After WWII, he became interested in the ethics of science and how a scientific worldview could guide moral actions (Bourgeois, 2013, p. 85-86; Jacobs, 2015, p. 250-252).

The horrors of WWII, particularly those stemming from the development and use of atomic weaponry, illuminated the values in science to its practitioners in an undeniable way. Not only did they recognize that the pursuit of particular endeavors had severe moral consequences,

the activities of a scientific discipline manifested certain values. Bronowski sees this creation of values as not just a product of science, but a core feature of human nature. As he explains it, "human beings create values and form an ethic because they direct their aspirations toward the command of nature, not as other animals, but by means of knowledge. To do this is a biological necessity for man and that which characterizes his nature as human nature. Man is the creator who must create values in order to elucidate his conduct and to learn from it, so he may direct it into the future" (Bio. Hum. Affairs, 1969, p. 3). Science is not unique in its ability to change nature. Instead, it is a powerful means by which humans fulfill their drive to inquire into their nature and try to shape their future. Yet WWII, for Bronowski, solidified that science is not an innocent activity. Specifically, science and technology can reveal humanity's capacity for cruelty on an enormous scale. "The values by which we are to survive are not rules for just and unjust conduct, but are those deeper illuminations in whose light justice and injustice, good and evil, means and ends are seen in fearful sharpness of outline" (Bronowski, 1964, p. 73).

The development of the atomic bomb, i.e. the Manhattan Project, was done in secret and Bronowski's writings indicate that he saw this as a fundamental flaw with the project. "A good society cannot be ruled by experts; it must listen to their advice, then rule itself… Crucial decisions about support for much research require perception of possible benefits and dangers" (Bio. Hum. Affairs, 1969, p. 3). The lay public did not have a say in the development or deployment of the atomic bombs at the end of WWII. Instead, it was developed by researchers and sanctioned by the government away from public eyes. The effects of the Manhattan Project were global and changed: conceptions of warfare, the possibility of causalities on a massive scale, and how science could be weaponized. Bronowski saw a relationship between the lack of public oversight of the Manhattan Project, the immorality of the deployment of the atomic

bombs, and the subsequent nuclear fallout. His solution was to enable the public to understand science, evaluate its benefits and dangers, and make informed decisions on the course of scientific research and the implementation of its products. Facilitating public understanding of, and involvement in, biological research became the work for the Council.

2.4 The Council for Biology in Human Affairs

The Council for Biology in Human Affairs was responsible for all of the Salk Institute's humanistic efforts. One of its foundational principles was that an informed public was essential to the integrity and proper functioning of professional biology. Some of the Council's work was related directly to public outreach whereas others focused more on national and international science policy. All of it was driven by the Council members' perceived ethical imperative to use biology as a means of promoting public welfare and involving the lay public in deciding what best served humanity's wellbeing. My focus in this section is how the members of the Salk Institute established the Council and its general organization. In the following section, I will describe the Council's specific efforts with respect to largescale public outreach.

Joseph Slater, the sixth President of the Salk Institute, took up his post in 1968 and held that title until 1972.[36] Slater was a former navy officer who enlisted after the bombing of Pearl Harbor. He was transferred to London after the war ended to develop plans for Europe's recovery. Some of his more notable assignments were Deputy United States Secretary to the Allied Control Council that governed Germany after its defeat and, later, Secretary General of

[36] The Salk Institute was founded in 1960. Jonas Salk served as president from 1960 – 1962. Gerard Piel filled in as president temporarily in 1962 after which Salk resumed the post until 1965. Augustus Kinzel relieved Salk for two years also taking on the title of CEO. Then Jerome S. Hardy agreed to fill in as president for one year and actively pursued hiring Slater. Slater then was hired in 1968.

the Allied High Commission after the Allied Control Council broke down. Upon returning to the US, he was appointed chief economist for Standard Oil Company as well as the Ford Foundation's international affairs program. Slater's appointment to the Salk Institute eased the concerns of its various sources of funding, including the National Foundation-March of Dimes which agreed to award the Salk a large grant if Slater stayed on as president for four years. This inspired the Gildred Foundation to award a large complementary grant (Bourgeois, 1969, p. 147; Jacobs, 2015, p. 337).

Despite the financial security Slater provided the struggling institute, Bourgeois implies that not everyone was happy with their new President. The junior scientists took particular issue with how Slater disrupted their creative, but disorganized, academic planning and administration of the Salk Institute (2013, p. 148). He hired staff to organize the curriculum, administrators experienced with grant-writing, and experienced institutional planners. Slater appeared determined to quickly create bridges between those in the Salk and those outside of it with special attention to businesses and government. Bourgeois states that some junior scientists chafed at Slater's oversight and insistence that the products of the Salk Institute be accessible and attractive (2013, p. 151). However, Jacobs portrays Slater's entrance as a relief to the Institute, but also disorienting for Slater. In Jacobs's account, Slater was responsible for making Salk's rose-colored future into a reality based on the rather disconnected ideas Salk had expressed (2015, p. 335).

Despite whatever discontent or relief Slater's appointment caused, he offered stability and advanced the Salk's ambitious missions. In his first year he put together a plan of action that clarified the Fellows' key wishes, which had gone unrealized until then. Three months after his appointment, the Board approved this plan, setting in motion the Institute's rapid development.

One of Slater's large early accomplishments was fulfilling one of the Fellows' core goals: to create faculty positions. One of the earliest faculty hires was Roger Guillemin who visited the Institute in February 1969. Slater impressed Guillemin sufficiently with his promise of a large oceanside lab space as well as his interest and competency in raising funds. Guillemin's acceptance of the position motivated the Salk Institute to commit to Slater's plan of action and hire five additional faculty members, one of which was Suzanne Bourgeois. In his second year, Slater officially established the Council for Biology in Human Affairs.

The Council was large, and its membership seemed to be in constant flux. Jacobs describes it as being "composed of twenty-five sociologists, law professors, psychologists, and scientists from the Institut Pasteur, Harvard, and other notable institutions, with funds of two million dollars" (2015, p. 335). However, this appears to be based entirely on a memo Bronowski wrote to staff members in 1970 prior to any official meetings or invitations.[37] These were proposed future members, many of whom Bronowski did not know or had not yet contacted. This is all to say that Bronowski, like Salk, had large plans and a vision for what the institute could become, but it was less clear how that future would come to fruition.

Over the course of its existence, the Council had many members in name who did not attend its meetings as well as many unofficial members who contributed to its work. As Bourgeois explains it, the Council "was to be the nexus of a network of individuals and organizations sharing their concerns about the consequences of the rapid progress being made in biology… the council counted international leaders from business, finance, and politics as well as distinguished scientists and humanists among its members" (2013, p. 163).[38] One of its core

[37] Jacobs refers to "Bronowski to staff, February 17, 1970" in the Jonas Salk Papers.

[38] The official representatives of the Salk Institute were: Bronowski, Holley, Luria, Monod, Salk, and Slater.

goals was to inform the lay public and empower its members to make decisions about the course of biological research. However, Jacobs reveals a different angle to the Council's goals. According to meeting notes, Bronowski said to a colleague that the Council would "form public opinion by informing it" (2015, p. 335). The implication being that the Council would present information to the lay public in a particular way that would lead people to have a particular interpretation of it. Perhaps Salk's method of treating members of the lay public as his peers would be untenable on the large scale at which Bronowski saw the Council as operating. However, it is notable that even in its infancy, the Council already was taking a position on how much the public could be expected to understand.

The Council did not just focus on public outreach. It comprised six commissions that fleshed out the multiple dimensions of the interrelation between science and society that Bronowski sketched in his "Biology in Human Affairs" statement. These commissions were: a) Biology in International Affairs; b) Biology, Ethics, and the Law; c) Biology, Learning, and Behavior; d) Biology in Contemporary Culture; d) Ecology, Environment, and Population; and e) Biology, Medicine, and Health Care.

While Bourgeois claims that the Council met often in either La Jolla or New York (2013, p. 164), there are only records of a few meetings that were dedicated strictly to the business of one of the commissions or the Council as a whole. While much of Bronowski's work for the Salk fit under the missions of the Council, much of it occurred prior to the Council's establishment. Nonetheless, it has been retroactively counted as part of the Council's activities. From the time the Council was established in 1970, it officially concentrated its efforts on: a) persuading *Time* magazine to write about, and sponsor, a health conference the Council would organize (1971); b) partially funding several "unusual" postdoctoral scholars who worked at the intersection of

biological research and public outreach (Bourgeois, 2013, p. 166); c) holding a meeting at Cold Spring Harbor on new developments in genetics research; d) conducting a seminar on the social implications of drug use; e) developing a series of seminar programs at the Aspen Institute for Humanistic Studies*; f) and continuing to apply for grants to fund additional faculty hires and the continuation of the Council*.[39] Jacobs corroborates my findings that the Council met rarely. She makes note of the seminars Bronowski organized as well as the health conference and the seminar on drug use (2015, p. 336).

2.5 The Council's Public Outreach Efforts

While Bronowski was the chair of Biology in Contemporary Culture, he was an active member of the other commissions on which he sat. This included the Commission on Biology, Ethics, and the Law. One of the few official meetings of this commission focused on the developments in genetics research, how the public might respond to them, and how to inform the public about the significance of these developments.

Stuart Ross, Jacob Bronowski's assistant, attended this meeting of the Commission on Biology, Ethics, and the Law at Cold Spring Harbor from June 11 to 12, 1971.[40] During this meeting, Ross took notes on the general topics of discussion and provided anonymized quotes on various topics. These topics included general concerns about the potential affordances of genetics research, cloning and reimplantation, prenatal genetic diagnosis, and gene therapy. He developed a classification system for organizing the comments people made in relation to these

[39] * These are instances in which Slater acted on his own. The following section will discuss the Aspen Institute.
[40] Bronowski was in the middle of making his acclaimed documentary television series, *The Ascent of Man*.

topics. His categories of classification were: “reasons for pessimism,” “reasons for optimism,” “action suggestions,” and “replies” to these categories. It appeared the Ross tried to reflect the exchanges between individuals by using a two-column format. On one side were the reasons for optimism or pessimism, and on the other side he wrote the replies Commission members gave to particular statements.

Ross did not provide a reason as to why he did not attribute the quotes to the individuals who made them. While Ross did not include a list of the meetings’ attendees, other notes reveal that Jacob Bronowski, Theodore Friedmann (an MD interested in genetic diseases), Richard Roblin (a political scientist), Abram Chayes (a Harvard law professor), David Bazelon (a Salk Institute trustee and appellate court justice), and several faculty from the Salk Institute were present. Because this meeting was not at the Salk Institute, but in New York, it is possible the entire body of the Commission was not able to attend and that other members of the Salk Institute who were not officially on the Commission joined as well. For example, while Jonas Salk was on almost every Commission, he was often unable to attend their meetings. Additionally, Bronowski had a tendency to invite people to meetings of the Council’s commissions even if they were not (yet) members themselves. This was the case for Friedman and Roblin, who Bronowski attracted to the Council through initial informal discussions and then through invitations to attend meetings. Shortly thereafter they had been named members of the Commission on Biology, Ethics, and Law.

Ross delivered this report on the Cold Spring Harbor meeting to Bronowski’s secretary with the instruction that it be delivered to all the members of the Commission. Along with the summary of the meeting, Ross noted in his accompanying commentary that the meeting was exploratory in nature on the reasons to be optimistic or pessimistic regarding the advances in

genomics. Ross added that he had not expected to come away with conclusions about the benefits and risks about genetics research. However, he did note that the meeting lacked *any* plans for how to do positive advocacy for the developments in genetics. The implication of this was that the meeting did not result in any plans for how to explain the significance of genetics research to the public. In the course of the meeting, the participants did *not* express urgency in addressing the ethical issues the topics of discussion raised. The participants did not develop plans for public outreach and dismissed claims that they ought to. They offered two kinds of reasons when they rejected a claim about the urgency of clarifying the scope or ethical significance of a particular advance to the lay public. In general, the discussants dismissed concerns because they thought either: a) with further experimentation and advances in genetics, the ethical issues would be resolved; and b) it would be unlikely that the public would have such an ethical concern or engage in behavior that would manifest the ethical dilemma.

When conducting this research, I found it unexpected that the Commission members were so dismissive of arguments that new genetics research raised pressing ethical issues and that they should be communicated to the public. A reason why I found this surprising was because the attendees also expressed that they had an ethical commitment to inform the lay public of the significance of advances in the biological sciences. For example, one member made an unchallenged statement proclaiming that because scientific research was at least partially supported by public funds, they had the responsibility of considering "the social consequences of the research" (Sum. CSH, p. 1).[41] The Commission members also agreed that scientists ought to have the burden of showing the necessity of their research.

[41] "Summary of the Meeting on June 11 & 12, 1971 at Cold Spring Harbor" sent by Stuart Ross to the Members of the Commission on Biology Ethics, and the Law.

There was, however, disagreement on how the public would react to potential future capabilities of gene therapy and pre-natal genetic testing. Some attendees were concerned that the public would react poorly to the advances in genetics research and would seek to restrict work in this area. Other members argued that it would be necessary to develop public information and outreach programs to inform the public of the real risks and benefits of these new areas of research. Yet these concerns were brushed aside when one attendee said that practitioners had already made efforts to communicate the significance of genetics research to the public. These efforts consisted of a single cover story in the April 19, 1971 issue of *Time* magazine. The meeting's attendees had not detected any sort of negative reaction from the public in response to this article and, therefore, did not think any immediate outreach efforts were necessary.

2.5.1 The *Time* Magazine Issue

Before continuing to describe what took place at the Cold Spring Harbor meeting, I will outline the *Time* cover story to which a member referred. This issue of the magazine is not particularly noteworthy on its own, in my opinion. The only reason I am going to discuss it at length is because the members at the Cold Spring Harbor meeting thought it was important. They thought it was so important that they cited it, and only it, as the reason why they did not need to engage in subsequent public outreach efforts. I believe the attendees' choice to use this cover story and its accompanying collection of articles as evidence to support an argument for them *not* doing more to develop public education programs is symptomatic of two issues among this group of scientists. First, they were not sensitive to the tone of the cover story, which introduced other

articles on genetics research, and how it portrayed this scientific work. This speaks to their lack of awareness of how media is consumed. Furthermore, it reveals how they did not consider how the media frames information and the great social context in which information circulates. Second, they thought that one article would be sufficient for informing the lay public about recent advances in biological research. This, perhaps, is an academic convention where a lab does not publish the same information over and over. One paper is enough to communicate the results of a study and disseminate them to their targeted audience. Disseminating educational information to a popular audience needs to occur over time through multiple outlets.[42]

I believe it is important to describe these articles because they were meaningful to Cold Spring Harbor meetings' attendees and because their choice to solely rely on this magazine issue to communicate the significance of genetics research was a mistake. By examining how the *Time* issue characterized these scientific advances, I aim to show how the Salk's humanistic initiatives were built on high hopes and shaky foundations. While the Council's goals were laudable, by looking at how its members pursued them, it is not surprising that they failed to achieve their objectives.

The title of the *Time* issue that a member referenced was "The New Genetics: Man into Superman." The cover depicts two orange double helixes superimposed over a nude man and

[42] An example of scientists doing this effectively was in the National Foundation for Infantile Paralysis' efforts to recruit volunteers and participants in their massive vaccine trial. The central organization first announced through its three thousand chapters which sent out letters to their members. They also reached out to the National Congress of Parents and Teachers; the National Councils of Jewish Women, of Negro Women, and of Catholic Women; and men from the Rotary Club, the Kiwanis Club, and the Chamber of Commerce. Throughout this, Salk was a public figure who gave public lectures and appeared on national television to talk about his efforts to fight polio. Journalists at well-read newspapers and magazines (e.g. *American* Weekly and *Time*) picked up on the significance of the vaccine trial and started conducting interviews with parents who had lost children to the disease. David Preston, a science writer at the Foundation, also developed the "Polio Pioneers" which gave children a button and a certificate after they received their inoculation. With these tangible efforts in place that clearly communicated the point of the research and its ethical significance, television, radio, and print news were able to create a narrative about how the lay public and the scientific community were joining together to save children. The Foundation did not rely on a single magazine issue to communicate with the lay public.

woman standing side by side. There arms are stretched above their heads and their arms are mostly obscured by the double helixes, creating the illusion of the figures merging into the DNA. Base pairs of amino acids act as censor bars. The first half of this issue of *Time* is devoted to reactions to the Vietnam War, disapproval of President Richard Nixon, and concerns about socialist uprisings in Latin America and, apparently, Berkeley. In the middle of the issue is the cover story heralding the "promises and perils" of genetics research. This initial article precedes subsequent essays outlining current research. The introductory article begins with an evocative quote from *Doctor Zhivago*:

> "Reshaping life! People who can say that have never understood a thing about life—they have never felt its breath, its heartbeat—however much they have seen or done. They look on it as a lump of raw material that needs to be processed by them, to be ennobled by their touch. But life is never a material, a substance to be molded. If you want to know, life is the principle of self-renewal, it is constantly renewing and remaking and changing and transfiguring itself" (Pasternak, 1957).

This is a striking quote because of the tension between genetics research and Yuri Zhivago's statement. Zhivago was a physician in the USSR who rejected socialism. In this moment in the novel, Zhivago has been unwillingly traveling with Liberius, an Old Bolshevik, and loses his patience with his captor's confidence that socialism can transform the lives of the oppressed for the better. In this quote, Zhivago expresses his belief that a life is not some substance that can be externally shaped, but something which transforms itself. Beginning an article on the advances of genetics research with this quote creates tension because there were, and still are, domains within this area of research that seek to change foundational structures of biology. For people like Bronowski and other members of the Commission, the structures of biology were also the structures of humans' morality and fundamental nature. Even if one were to dodge the question of the relationship between genetics and human nature, the field of genetics *does* investigate biological *material* that they posit is a central component of biological

life. Zhivago's statement, when placed in the context of genetics research, seems to function as a caution against the interventionist aims of this area of biology.

The article continues by quoting one of the architects of the biological revolution, Robert Sinsheimer. He proclaims that in light of scientists having an increased understanding of genetics, they now understand the origin of life and have the ability to design humanity's future. The article proceeds by reflecting on the potential genetic damage caused by the radiation from the atomic bombs dropped at the end of World War II before quoting Theodosius Dobzhansky's ethical dilemma: "If we enable the weak and the deformed to live and to propagate their kind," he says, "we face the prospect of a genetic twilight. But if we let them die or suffer when we can save or help them, we face the certainty of a moral twilight" (*Time*, 1971, p. 53). This juxtaposition of the atrocities of WWII and the idea of genetics research being able to mitigate the lasting damage would have been was an appealing image to the founders of the Salk Institute, particularly Bronowski. Bronowski begins *Science and Human Values*, a collection of lectures on the value-laden nature of science, describing his experience of Nagasaki after the bombs fell at the end of WWII. In the preface of the book, Bronowski reflects,

> "When I returned from the physical shock of Nagasaki… I tried to persuade my colleagues in governments and in the United Nations that Nagasaki should be preserved exactly as it was then. I wanted all future conferences on disarmament, and on other issues which weigh the fates of nations, to be held in that ashy, clinical sea of rubble" (Bronowski, 1964, p. xiv).

At the beginning of "The Creative Mind" essay, Bronowski describes his experience of driving to Nagasaki Harbor to join a military ship after landing on an airstrip some ways away. He was part of a team of British civil engineers and scientists tasked with documenting the fallout from the atomic bombs. He recounts that he was unaware he had entered Nagasaki until

he heard music coming from the ship in the harbor. It was then that he recognized the things he thought were collections of broken rocks were destroyed buildings.

> "The moment of recognition when I realized that I was already in Nagasaki is present to me as I write, as vividly as when I lived it. I see the warm night and the meaningless shapes; I can even remember the tune that was coming from that ship. It was a dance tune which had been popular in 1945, and it was called 'Is You Is Or Is You Ain't Ma Baby?' These essays… were born at that moment" (Bronowski, 1963, p.3).

Despite the horror he experienced at witnessing the aftermath of the bombing of Nagasaki, Bronowski clarifies that this event was not novel nor was this the first time humanity had grappled with the morality of science.

> "The power of science for good and for evil has troubled other minds than ours. We are not here fumbling with a new dilemma; our subject and our fears are as old as the tool-making civilizations. Men have been killed with weapons before now: what happened at Nagasaki was only more massive… Nothing happened in 1945 except that we changed the scale of our indifference to man; and conscience, in revenge, for an instant became immediate to us. Before this immediacy fades in a sequence of televised atomic tests, let us acknowledge our subject for what it is: civilization face to face with its own implications. The implications are both the industrial slum which Nagasaki was before it was bombed, and the ashy desolation which the bomb made of the slum. And civilization asks of both ruins, 'Is You Is Or Is You Ain't Ma Baby?'" (Bronowski, 1964, p. 4).

Bronowski identifies his experience in Nagasaki as being the catalyst for his recognition that science, and biology in particular, can reveal essential human values, the guidance of which could steer humanity away from war. In his recognition that he was in the center of the destruction in Nagasaki, he was struck by the double horrors which technological advances had produced. On the one hand, the city had focused on using its technological skills to produce bombs, military planes, ships, and other weapons. On the other hand, after the bomb was dropped, the city revealed the atrocities that nuclear technology could produce. Nagasaki, for Bronowski, can be seen as a manifestation of a crisis of morality that is inextricably interwoven

with science. He sees the city in both contexts as being in ruin – ruins which are the offspring of a civilization that has not confronted the ethical dimensions of the physical sciences and the technology which its findings enabled.

Bourgeois identifies that the atomic bombs shaped how the other founders of the Salk Institute saw the role of science in society. In her account, she describes in detail how both WWI and the militarization of science in WWII affected each of the founders. In every case, she reveals how WWII, in particular, shaped the careers of these men. Bourgeois reveals the fraught relationship its founders developed with the physical sciences and how they saw the biological sciences as a means of ameliorating the devastation caused by nuclear research. She begins her historical account by describing the impact of WWII on its founders.

> "It is poignant that, by the fortunes of war, Dulbecco was with the German army on the Russian front, whereas Cohn was with MacArthur in the Philippines and Bronowski was seeking the maximum destruction of Germany while Weaver was working on shielding London. It is ironic that Cohn and Bronowski were involved in reporting on the effect of bombs that Szilard and Lennox took part in building. Meanwhile, Monod and Crick were in harm's way and interrupted their careers to protect France and England from Nazism and destruction. All had horrendous experiences that were to change their lives and transform the world, and the painstaking war-oriented flu vaccine of Salk was to lead to the successful polio vaccine and to the creation of an institute that would contribute to making our planet a little more livable in the atomic age" (Bourgeois, 2013, p. xxxiv).

Returning to the *Time* magazine cover story: it is striking that, given the founders' experience with atomic weaponry in WWII, the attendees of the Cold Spring Harbor meeting saw this introductory article an accurate conveyance of how the scientific community views their own research. For context, one member stressed the need for public outreach to prevent "a strong likelihood of over-reaction by the public and by the government as these potential developments become known" (Sum. CSH, 1971, p. 2). "These potential developments" referred to the advances made in pre-natal genetic testing, the possibility of gene therapy, cloning, and in vitro

fertilization. Another member responded "There has already been a fair amount of publicity for example the recent *Time* cover story. But where has been the over-reaction?" (Sum. CSH, 1971, p. 2).

The article's juxtaposition of how the atomic bombs caused irreparable genetic damage with scientists contemplating ethical decisions that would impact the trajectory of our species is unsettling. The article does not communicate any panic on the part of its author or provide their readerships' possible reactions to this information; however, the presentation of the dangers of genetics research is sensationalistic. At least it appears sensationalistic from the standpoint of the present in which researchers do not have the same influence over policy, nor are genetic tests and treatment as straightforward as these early geneticists imagined. Today, the idea of being able to share someone's memories by taking a pill with portions of their DNA is laughable. However, because *Time* had, and has, a reader-base in the millions that viewed the magazine as a reliable source of news, its presentation of scientific research carries weight. While many readers may not have regarded *Time* as a source of scientific fact, the magazine has prided itself in earning the public's trust and upholding standards of journalistic integrity.[43] The magazine, during the 1970s, positioned itself as anti-socialist and focused on global political issues as well as other matters of public interest. The cover story of the issue prior to April 19th one was focused on the court marshalling of William Calley, a US army officer convicted of murdering South Vietnamese civilians. The subsequent issue focused on the exchange of Chinese and US table tennis players during the championship games in Japan of that year. The topics of other cover stories during 1971 included: Richard Nixon, Jimmy Carter, espionage, Joe Colombo (crime family boss), suburbia, Pakistan refugees, and air conditioning.

[43] See *Time* Magazine's description of its commitment to the public: http://time.com/longform/join-time/

The magazine has been regarded as a source of serious news and not as being unreliably biased or as a tabloid. Because of this, its portrayal of genetics research as being akin to Cold War socialists' alleged aims of oppressively reshaping humanity could trouble a reader. Additionally, in the anxious global atmosphere caused by two nuclear superpowers staring down the barrels of their missile launchers at each other, the article's reference to the genetic effects of atomic warfare could come across as fact. The article's awareness of literature and political events could give the claims about genetics research merit, despite their inaccuracy.

The ending of the article does not correct the image of genetics research leading to a world where detached scientists make ethical decisions that affect the entire human race. Instead, it concludes ominously. It warns that humanity may wind up as Faust did, finding that in exchange for his power over life, he has bartered its soul to the devil. This conclusion evokes images of Soviet oppression in which men clinically weigh matters of enormous moral consequences while eternally corrupting themselves in their pursuit of knowledge through any means necessary. This a particularly powerful image given that this issue was published during the Cold War and the Vietnam War. By 1971, the Soviet Union had established itself as a nuclear equal with the United States, but both worked throughout the 70s to curb nuclear proliferation. Despite this détente, both superpowers continued to jostle for control over the international political landscape and this was reflected in this issue of *Time*. The majority of the stories, both before and after the cover story, are devoted to stories about events related to the Cold War and its politics. Casting genetics research as a black-or-white ethical dilemma by using a Faustian metaphor within the context of commentary about the Cold War continues to link advances in research with the bogeyman of communism.

The following journalistic pieces are less grim. One provides an account of Watson and Crick's work on DNA and the questions in molecular biology that remained "largely unanswered" 18 years after the postulation of DNA's basic structure (*Time*, 1971 p. 54). Another speculates about the future of neo-natal treatment of genetic conditions in which doctors could use "laser beams to slice through DNA molecules" (p. 59). Others focus on the possibility of RNA viruses as a cancer treatment, pills that transmit memories, and ethical nightmares produced by human cloning.

Despite the relative optimism of the articles following the introductory essay, the image of the ethically ambivalent and powerful scientist does not disappear. One notable feature of the subsequent articles is that the scientists they discuss are portrayed as not being affected by their social contexts. Crick's reported exclamation "we have discovered the secret of life!" does not come across as someone comprehending the ethical significance and dangers of genetic research. Instead, it is presented in the context of two young men celebrating at a pub frequented by Cambridge scientists, detached from the everyday life of the lay public. It does not provide a portrait of Crick as a man, who was a physicist by training, that had his life interrupted by WWII when a bomb destroyed the apparatus he was using to study viscosity. Nor does it describe his work as a scientist in the Admiralty for which he designed weapons. This essay does not describe his life before his work with Watson at all, let alone his motivation for switching to biology. Like many of the founders of the Salk Institute, Crick's experiences in WWII led to his interest in biology. Crick had questions about the origins of life and since he did not accept a religious explanation, he looked for a scientific explanation. The switch from designing lethal weapons to wanting to understand life itself is a remarkable aspect of Crick's career (Crick, 1993). These

biographical details make it difficult to retain an image of Crick as a scientist removed from the everydayness of the world.

2.5.2 The Council's Additional Efforts

Returning to the meeting at Cold Spring Harbor: its attendees were apparently aware of the *Time* cover story, yet did not take exception to the presentation of genetics research. I contend this was a grave oversight on their part that reveals their disconnect with how the lay public perceived the significance of genetics research. Furthermore, this oversight speaks to their lack of awareness of how the lay public consume media.

They may have not considered the tenor in which the article conveyed the information because it accurately presented the details of the research. The speculations of how these advances could be used to cure cancer and treat neo-natal conditions reflected the tentative conclusions members of the research community had reached. The articles even took pains to explain foundational concepts in molecular biology and genetics. However, the attendees seem to have not be as aware of how *they*, the scientific community, were presented and how this could affect how the public could perceive the likelihood of the ethical dangers associated with genetics research coming to fruition. This is not to say that the Commission members were unaware of the ethical issues that were involved with genetics research itself. In fact, the members of the Cold Spring Harbor meeting raised potential ethical issues posed by genetics research that indeed manifested are still-unresolved concerns in the 2010s.

Because many issues that the attendees made apparent in this meeting have not be resolved, it is illuminating to see how the attendees of this meeting dismissed the urgency in

communicating them to the public. On the topic of prenatal genetic diagnosis, something which is relevant to Lab X, the participants raised concerns about how people would retain privacy over their genetic information during and after their physicians' diagnostic work. At least one member raised the issue that there would be files of people's genetic information and that determining who would have control over the use of the information would be important for preventing the misuse of this data. In response to this concern, other members stated that this was a "present controversy" that would probably lead to better means of protecting genetic information (Sum. CSH, 1971, p. 9).

There was also a split among attendees regarding how the public would respond to the availability of pre-natal genetic testing. One subgroup within the Commission argued that the technology used to determine whether a fetus had a particular genetic disorder could also be used to determine what "trivial" characteristics fetuses had, such as eye color. This camp was concerned that if parents were able to determine this information, they may choose to abort fetuses due to superficial preferences (e.g. eye color). While this was quickly dismissed as something that people would be unlikely to do, Commission members found it more difficult to resolve the issue of people having abortions in response to discovering a fetus had a genetic condition, aborting it, and then a cure being developed for that condition shortly thereafter (Sum. CSH, 1971, p. 8, 10). The opposing group did not see a relationship between technology that advanced diagnostic capabilities without providing treatment options, and a potential increase in the rate of abortions. Those who saw only the promises of pre-natal genetic testing saw the alleged social consequences of this technology as "not problems with prenatal diagnosis; they are problems with abortion. Society must make up its mind about abortion first and then use prenatal diagnosis accordingly" (Sum. CSH, 1971, p. 10). However, the other side responded that the

development of this new technology aggravated concerns about abortion and could lead to significant public confusion.

The meeting ended with unresolved differences in perception of possible public confusion. Specifically, the members came away with different positions on the relationship between new technologies and pre-existing disagreements on the ethics of particular medical interventions. Nonetheless, the Commission members were in agreement regarding its next actions. They unanimously agreed that their most important task would be to "design institutions which can monitor the situation [regarding the advancement of genetics research], anticipate problems, and deal with them on a regular basis" (Sum. CSH, 1971, p. 13). They agreed that they needed a permanent staff that would keep both Congress and the public informed by presenting the benefits and dangers of genetics research. The greatest challenge they saw to the Commission's work would be implementing communication between, and regulation of, scientific communities. They wanted to facilitate scientists adapting to public determination on how to proceed with research and also enforce that scientific communities went along with the lay public's wishes. The members of the meeting spent little time discussing how, exactly, the public would become informed. The most concrete proposal for public education was for the establishment of a "Council of Wise Men" who would recommend actions and consider the implications of scientific advances for society. They would also be tasked with educating the public. However, this was met with several objections including doubts regarding the Council of Wise Men's methods for generating action.

While this meeting ended on a promising note, albeit with unresolved disagreements, it did not lead to any significant public outreach efforts or the establishment of institutions that would interface between scientific communities, governments, and the public. Instead, the

Council developed a relationship with the Aspen Institute for Humanistic Studies, a non-profit think tank. This relationship developed because Slater had been working since 1968 to both secure the significant funding the Salk Institute needed as well as make meaningful bridges between the natural sciences, the humanities, and social sciences. Slater also took on the role of president for the Aspen Institute and decided to split his time between the two institutions (Bourgeois, 2013, p. 156). This enabled the Council to pursue its goals of facilitating public education in collaboration with an institution that had more experience in communicating with those outside of the academic organizations.

Because of the Salk Institute's connection with the Aspen Institute, their public outreach efforts moved away from Bronowski's more philosophical considerations and, instead, became applied and commercial. The Council's efforts took the form of a seminar that advanced the aims of the National Commission on Marijuana and Drug Abuse (NCMDA) as well as an "executive seminar program" in Aspen.

In the summer of 1971, Bronowski, other members of the Council, and Slater began to discuss the NCMDA and ways in which they could contribute to it. They saw drug use and addiction as a clear intersection between the biological and the social. Involving the Council in this large federal initiative would be a way to show how the biological sciences could speak to issues of societal significance. The Secretary General of the Council, Harry Boardman, sent a follow-up message to Salk on September 20, 1971 summarizing a conversation they had about how to contribute to the national conversation on the possible dangers of marijuana usage and drug abuse. This conversation sketched the scope and budget of "a small study seminar for scholars and men of public affairs." This study was eventually funded through a joint effort of the National Institute of Health and the National Science Foundation. After further planning

meetings in March 1972, the Council held its study from October 21 to 23, 1972, titling it "The Changing Status of the Young." They held it at The Hotel Del Charros, a wealthy resort hotel in La Jolla that was known for its discretion and accommodation of politicians.[44] While the proposal called for 10-12 participants, the actual meeting comprised 16, including Jacob Bronowski, who served as moderator.[45] The attendees consisted of prominent academics, civil servants, or public figures. The stated goal of the seminar was "To develop a body of thought which may advance generally understanding of contemporary America and which might thereby inform the particular concerns of the [NCMDA]: the analysis of the complex influences which have encouraged drug abuse and recommendations which these analyses suggest" (Remarks, 1971).[46]

While the meeting was intended to address concerns relevant to the NCMDA, the actual conversations that took place had a wider topical scope. Some topics of discussion were: the effects of the atomic bombs on Hiroshima and Nagasaki, science and human values, Bronowski's own writings including *The Abacus and the Rose*, *William Blake and the Age of Revolution*, and *The Identity of Man* (Tr. of Mar. Conf., 1972).[47] Even though in the initial proposal for the seminar, Boardman said that they would meet two or three times, the three day gathering in October 1972 was the only meeting the Council would hold on marijuana and drug use. While this meeting did not lead to more publicly accessible educational efforts, it did result

[44] It was torn down in the early 1970s shortly after the Council's meeting to make way for condominiums.
[45] The meeting attendees were: Joseph B. Adelson (psychology professor from the University of Michigan), John J. Conger (past president of the American Psychological Association), Brig. General Robert E. Gard Jr., Benson E. Ginsburg (behavior geneticist), Chad Gordon, David Gutmann (photographer and painter), Michael Jacobson (microbiologist), Louis Judd (prominent psychiatrist), Edward Kalachek (professor of economics at Washington University in St. Louis), Phyllis La Farge (author), Robert Reischauer (economist), Joseph Rhodes (politician and activist), Jonas Salk, Norman Scotch (Founding Dean of Public Health at Boston University), and Roy Wehrle (diplomat).
[46] "Remarks: Per our conversation," dated September 19, 1971, sent via route slip on September 20, 1971, to Jonas Salk from Harry Boardman.
[47] "Transcript of Marijuana Conference," October 21-23, 1972, The Hotel Del Charro, La Jolla, CA.

in a report which was sent to the NCMDA Commission. In subsequent intra-lab messages from Boardman, Ross, and Slater, they noted that the ultimate recommendations that the NCMDA put forth were in agreement with the conclusions at which the Council arrived.

The seminar study for the NCMDA was one of the few concrete initiatives that the Council undertook without support from the Aspen Institute. Slater more consistently attempted to advance the aims of the Council through his affiliation with the Aspen Institute. His work took the form of a series of "executive seminars." These seminars were marketed toward business leaders as opportunities to interact with "key persons from other sectors of society" including UN agencies, private philanthropic organizations, academics, and members of the judiciary (Slater & Anderson, 1972, p. 1). Despite Slater's position as President of the Salk Institute, there were no Salk scientists who participated in the executive seminars. Nonetheless, the Council regarded these seminars as working toward its mission of educating the public on science and its humanistic and ethical values. While Salk faculty and fellows were generally supportive of the work Slater was doing with the Aspen Institute in principle, his absence led to feelings of disorganization and abandonment. This is reflected in correspondences within the Institute that were attempts to schedule meetings between Salk, Cohn, and others. It appears that Slater's presence provided some organizational structure to the Salk Institute. Bourgeois also notes that Slater accepting the position in Aspen shook the Salk Institute because it was still developing itself as a stable organization and it needed the attention of a creative administrator (Bourgeois, 2013, p. 159).[48]

[48] Bourgeois speculated that Slater realized soon into his tenure as president of the Salk Institute that he did not want to remain in academia. She believed that he wanted to become influential in international politics and business. The position at the Salk Institute would serve as a useful stepping stone (Bourgeois, 2013, p. 159).

In the summer 1972, the Aspen Institute held nine in-residence, two-week seminars that attracted almost 200 people. These seminars were different than the workshops and conferences the Aspen Institute also put on. The seminars were open to an affluent segment of the population for a price. On the other hand, the Aspen Institute itself funded the workshops, which were attended by invited guests consisting of prominent academics and policy-makers. The seminars provided information and networking opportunities to their participants but did not solicit the opinions of this portion of the public regarding the course scientific research. These were, instead, opportunities for education and developing connections between industry, and policy-makers, and academics. The workshops, on the other hand, served as a basis of policy recommendations. Notably, there were no members of the lay public in attendance at these invited workshops. In 1972, the Aspen Institute organized: a seven-week workshop led by a core group on energy sources and the potential scarcity of energy in the future; a multi-week workshop on the benefit of developing a new institution designed to analyze public policy choices; a meeting on university financial planning challenges; a month-long workshop on the government and media; and several multi-day conferences on non-US perspectives. The workshop on energy sources led to a paper presented to the United Nations Conference on the Human Environment held in Stockholm that year.

It is notable that while Slater's position at the Aspen Institute satisfied the Council's aims of educating the public on current advancements in scientific research and making recommendations on the course of subsequent research, they were not pursued in the spirit which guided Salk and Bronowski to work with Slater to establish the Council. One of the key tenets that Bronowski and Salk saw as being fundamental to biological research pertain to the function

of an informed public. I repeat and expand upon my previous quotation of Bronowski to draw emphasis to the centrality of public outreach to the broader mission of the Salk Institute,

> "Human welfare depends upon fundamental research and study for the knowledge essential to it and upon the responsible dissemination and direction of that knowledge so that the public, not the researcher, can make rational choices in favor of good and against harmful applications. A good society cannot be ruled by experts; it must listen to their advice, then rule itself. But to question, to test, to judge the advice of the expert is possible only for an informed population. Nor can a good society wait upon discovery to obtain an informed public. Crucial decisions about support for much research require prior perception of possible benefits and dangers" (Bio. Hum. Affairs, 1969, p. 3).[49]

In this excerpt, Bronowski proclaims that because biological research promotes human welfare, the public has an inherent right to know about it. For researchers, it is an ethical obligation for them to explain their work, and its implications, to the public so that *the public* can choose how it is used in society. Not only do researchers have an obligation to educate the public on the nature of biological research, but they also have an imperative to communicate to lay audiences how their research "directly affects human values," which are "an integral part of human nature" (Bio. Hum. Affairs, 1969, p. 2, 1). Significantly, these values are not independent of human biology, but are part of "the biological nature of man" (Bio. Hum. Affairs, 1969, p. 1).

Bronowski and Salk wanted to educate the public on biological research so as to enable its members to make decisions about matters which affected their physical welfare. They also wanted to make clear to the public how the values of biology, and the activities of biological research, reveal aspects of human nature itself. The seminar programs for executives and the workshops that prominent academic attended pulled apart this foundational goal of the Salk Institute's humanistic program. By doing so, the Aspen Institute worked against the Council's

[49] This is in the statement, "Biology in Human Affairs," Bronowski drafted with input from Salk. While Salk provided some feedback, the tone in which this statement is written is very much that of Bronowski. This, and versions of this statement, appeared in the grant Bronowski submitted to the Russel Sage Foundation.

mission to ensure that the public could make informed decisions about the direction and application of biological work. At the Aspen Institute, policy recommendations still came from the elite and highly educated. Furthermore, members of the lay public did not receive education on contemporary research for free. Instead, they would have had to possess the financial resources to pay for two-week seminars and be in a position where they could afford to take this time away from their jobs. Additionally, they would have had to work for employers who would understand the value of attending these seminars and who gave their employees flexibility with regard to how they took vacation time or just time away from work.

2.6 The Minimal Public Impact of the Council

The Council did not have the lasting national impact that Bronowski, Salk, and Slater envisioned. This is for several reasons, two of which I have already described in the previous section but did not flag as such. The first, and probably most significant reason, was Bronowski's death in 1974. All accounts of Bronowski depict him as a force of nature and a one-man show. While he had substantial logistical assistance from Stuart Ross, Bronowski was the driving force behind the Institute's humanistic efforts. By this time, Slater had left the Salk Institute as President and had been replaced by Frederic de Hoffmann in 1972, who, according to Bourgeois, was not supportive of the humanistic mission of the Salk Institute. Jacobs paints a different picture of de Hoffmann. According to her, he froze salaries, stopped recruitments, and sold off non-essential property to keep the institute's doors open. The Board of Trustees did not step in to help with the Institute's financial crisis because, Jacob's speculates, O'Conner and Salk's falling out (Jacobs, 2015, p. 350). Whether de Hoffman was the tyrant Bourgeois depicts or the

desperate administrator confronted with a willfully disinterested Board of Trustees, his tenure as President marked the end of the Institute's public education efforts. After Bronowski's death, the Council was dismantled, the Szilard Memorial Collection of books were sold, and all of Bronowski's other projects were terminated (Bourgeois, 2013, p. 178). Coupled with Salk's growing distance from the Institute after Slater's departure, there was no longer the momentum to continue the large public outreach projects the Council undertook.

Two additional reasons for the minimal lasting impact of the Council on public perception of science can be best summarized as: 1) a lack of time; and 2) a lack of awareness on the part of the members of the Salk Institute. Bronowski was the only Fellow who was hired because of his humanist interests. While the other Fellows, scientists, and faculty were generally supportive and committed to the humanist initiatives their institute undertook, they were not hired to participate in endeavors like the Council. Their sole job was to conduct research, acquire grants, and train junior members in their labs. Any of the work the Fellows did on the Council's commissions was during their own minimal spare time. In many ways, it is understandable that the Council boasted so few actual attempts at educating the public – its members were stretched too thin. In the background, from 1960 – 1972, the Salk Institute encountered many difficulties acquiring sufficient funding to build their impressive buildings, hire staff and faculty, and outfit the Institute with cutting-edge equipment. The Fellows and scientists were under significant pressure to continuously acquire funding for their individual labs and produce research which justified their place at the Salk.

Bronowski and Salk had wanted to hire social scientists to become an interface between the scientific world and the public, but this never came to fruition. They had actually received a grant from the Russell Sage Foundation prior to Slater taking over as President. In their grant

proposal, Bronowski and Salk proposed that they would hire, initially, a handful of social scientists. These social scientists would train with biologists at the institute for six months and then begin identifying how biological research addressed social issues. The social scientists would also conduct mandatory seminars that the faculty and scientists would attend. This would allow the social scientists to train biologists to recognize the social and ethical implications of their work. What Bronowski meant by "social scientists" is unclear. He did not provide examples. His rationale for wanting to hire social scientists was that they would be most familiar addressing social issues. It is unclear what kind of social scientists he would have had in mind because sociology was dominated by Mertonians at this point. Bronowski wanted social scientists to examine biological practice, its results, and say how these addressed, or could address, foundational questions about society, ethics, and human nature.[50] The Foundation was displeased with the use of their funds and sent Slater a letter, who in turn then sent it Salk with the marginal notes he added (and described below):

> "We had hoped that our funds [arrow with vertical line in margin] would lead to the development of a research program at the Salk Institute similar in character to other domains of activity that are being pursued there. We also hoped that the Salk Institute would become a center, hopefully a center of influence, for persons concerned with the interface [arrow with vertical line in margin] between the social and life sciences – a setting in which they could both work and study. We are disappointed in the program up to now. While the Council for Biology in Human Affairs may prove very valuable, it is not a replacement for the kind of group and the kind of program that we had hoped to stimulate and develop by our funds. Moreover, while visitors are often exciting to persons in other fields, we see little purpose of [two lines in margin] a long run in the expenditure of our funds for supporting primarily visiting scholars" (Orville Brim, President of the Russell Sage Foundation to Joseph Slater, September 28, 1970).

There is no description of why the Salk Institute established the Council with the Russell Sage Foundation funding as opposed to hiring a research group of social scientists. There are a

[50] I would argue that the job him envisioned these social scientists doing would be closer to what contemporary STS scholars do.

few charitable interpretations of why the Institute did not establish their proposed lab of social scientists. It may have been easier to organize scientists with whom Bronowski and Salk were familiar than to determine what was happening in the social sciences at that time and figure out how to integrate them into a biology research institute. Or it is possible that despite explicitly stating they would hire social scientists with Russell Sage Foundation funding, they saw the large network of Council members as going above and beyond the achievements they promised in the grant proposal – therefore perhaps they thought it was unnecessary to develop a social science research unit at the Salk. A more skeptical reading would be that the Salk Institute never really intended to hire the cadre of social scientists. It may have been a way of making their grant application more attractive. They may also have not done the necessary research prior to submitting the application to determine what social scientists in the 1970s actually did. Slater's marginalia and annotations indicate that he took Brim's complaints seriously. It is notable that he sent a copy of the marked-up letter to Salk. Perhaps he did so to highlight key parts for Salk to read or to communicate what he believed were serious issues.

Despite Slater coming onboard, this social science research group never took shape at the Salk Institute. In 1972, Ross (Bronowski's assistant) wrote to Boardman (the Secretary General of the Council), returning to the idea of the Russell Sage Foundation grant saying that they could apply for another grant to "provide an opportunity to open the way to initiating and then expanding work in the social sciences at The Salk Institute" as was the original intent of the first Russell Sage Foundation grant (March 13, 1972). Yet with the amount of time Slater had been spending at the Aspen Institute and his impending departure, there was no real administrative

support to try to pursue this initiative again.[51] Then de Hoffmann's presidency heralded an end to the Salk's expansive public education agenda.

The second possible reason why the Council had little lasting impact on the public's understanding of science is that the members of the commissions had little awareness of how the public perceived science. As the meeting in Cold Spring Harbor reveals, the commission members were unaware of how a lay audience would view genetics research within the context of the Cold War, the Vietnam War, and lingering anxieties from WWII about scientists altering human life. Additionally, the Council never did any assessments of the lay public's perceptions and understandings of biological research, nor did they hire anyone to do this work. Perhaps this would have changed if the Salk Institute had hired the social science research group described above. However, despite the celebrity that many members of the Salk Institute had acquired in their careers as scientists or public intellectuals, none of them had experience communicating the significance of science to the lay public. While Bronowski had written books explaining science to non-scientists and had written and presented the television series *The Ascent of Man*, Bronowski was only one person and intentionally offered accounts of the history of science that were in his "personal view." By this, I mean that Bronowski was more interested in explaining the significance of the activity of science as a pursuit toward a goal, which he argued was the same goal of artistic pursuits (1964). He was not as interested in explaining for what particular technologies were used or how they were developed. Nor was he interested in imparting scientific knowledge. Instead, the entire focus of his communication to the public was regarding

[51] Slater officially left the Salk Institute in February 1972; however, he had been looking for his replacement for quite some time. In May 1971, he had proposed de Hoffmann as his replacement, who was elected as Chancellor and CEO in August of that year. In February 1972, de Hoffmann officially took over from Slater.

the moral dimensions of science and how its practice reveals what values humans hold and which ones they prioritize above others.

While Bronowski's perspective was valuable to the Salk's public outreach initiatives, it abstracted away from the everyday realities of science and simplified the debates and dissents for the sake of telling a cohesive narrative. Additionally, he was only one person and the task of educating the public on the significance of contemporary biological research was too big even for the larger-than-life public intellectual that was Jacob Bronowski.

2.7 Conclusion

In concluding this section, I will analyze the failed attempts of the Council drawing on the concept of "revolution" as it has been used as a technical word in STS and the history of science. By doing so, I aim to articulate some relevant differences between professional biology of the 1970s and professional biology during and immediately after the Human Genome Project. The kinds of differences on which I will focus are structural features of professional biology during these two time points those that promote or limit its practitioners to communicate with the lay public. Ultimately, I will conclude that the biologists of the 1970s who had lived through WWII experienced an ethical imperative to communicate the significance of their work to the lay public despite their lack of time and communicative training. Even though the Salk Institute failed to enact a revolution that would transform biology into a field that would address social issues while educating the lay public, their humanistic motivations still affected the agenda of professional biology. While I would argue that the emphasis on communication and ethics is a

part of biological practice, the practical realities of biology in the late 2010s precludes biologists from mounting largescale public outreach initiatives.

From the 1971 meeting notes at the Cold Spring Harbor meeting, there was a sense of optimism about the future of genetics research. Watson and Crick had already modeled the structure of DNA, in 1953, revealing its semi-conservative nature and how replication occurs. Even though researchers were still trying to determine how DNA controlled the behavior of cells, practitioners were optimistic that once this problem was solved, it would be a fairly straightforward process to developing techniques to correct genetic conditions. It is clear that the meeting's attendees had high hopes for what genetics research could accomplish in the near future. The optimism must have seemed even more justified when advancements throughout the 1970s led to Kary Banks Mullis's development of the polymerase chain reaction in 1983 which allowed researchers to quickly isolate sections of DNA. By 1986, Salk scientists, including Renato Dulbecco, as well as Watson and Sinsheimer were strategizing how to sequence the whole human genome. By 1990, the Department of Energy and the National Institutes of Health had signed on to fund this international undertaking for the sake of provide a complete sequence of the DNA base pairs comprising the human genome. A key motivation for doing so was to improve medical tests for diseases and to better understand genetic conditions. Many of the Salk Institute scientists and those they trained were involved in this research and focused on childhood genetic conditions. This was a natural continuation of an early motivation for founding the Salk Institute which was to develop treatments and preventatives for little-understood conditions. Genetics research seemed to be the key to understanding the mechanisms behind diseases and conditions. Developing genetic models of these conditions was a crucial step in doing so.

One effect of the Human Genome Project was that animal models of human diseases were defined in terms of their genomes and their genetic variations, as opposed to behavior. Because there are important differences across the genomes of different species, biologists working in disease-related research focused on particular organismic models. This created the new problem of how to integrate the findings from one organismic model with those from a different organismic model. In short, biologists began to specialize to a greater degree during the 1990s and through the early 2000s. As the next chapter will describe in greater detail, biomedical researchers began to further specialize, developing expertise in particular "lines" of models of a particular species. This specialization created additional challenges for researchers who wanted to integrate their findings across animal "model lines" for the purpose of creating a more complete model of a human disease. A problem that biologists studying diseases faced was communicating to the public how a particular line of animal model reveals something about a human disease. They also faced the problem of communicating this to labs which studied the same aspects of the same disease, but with a different model line. This is a markedly different communicative concern than those sketched in the Cold Spring Harbor meeting. Before even being to communicate the significance of biological research to the lay public, practitioners first had to communicate this to their professional peers working with different organismic models. This continues to be an ongoing challenge in contemporary biology that is not easily solved.

Through this period of expansion and specialization in biology, there were growing concerns about the lay public's trust in the authority of biological research. Gregory Petsko, a biochemist who works on neurological conditions, has also captured a fieldwide concern that the lay public is increasingly skeptical of the ethics of genetics-focused biological research (2002). As of the 1970s, there was not yet the feeling that the lay public did not trust the authority or

ethical integrity of biology. As of the late 2010s, this perception had most certainly changed. The March for Science in 2017 represented that there was "a broader perception of a massive attack on sacred notions of truth that are sacred to the scientific community" (Mooney, 2017).[52] Overall public confidence in science has remained pretty much unchanged since 1973; however confidence in scientific work regarding vaccinations and climate change has decreased since the 1970s (Metz, Weisberg, & Weisberg, 2018). The policy changes after the November 2016 election have also given a platform to those skeptical of science. These changes include the Trump administration's discrediting climate change and weakening of environmental protections. Supporters of science and evidence-based policymaking have concerns that the federal government's skepticism toward consensuses in scientific communities is empowering the anti-vaccination movement. In 2019, the World Health Organization named "vaccine hesitancy" as one of the ten threats to global health (WHO, 2019). Since 2009, there has been a significant increase in the number of people who hold anti-vaccination views and a growth in the number of states that allow for non-medical exemptions for people who choose not to vaccinate their children (Olive, et al., 2018). This paired with Trump's meeting with Andrew Wakefield, the author of the debunked paper linking childhood vaccinations and autism spectrum disorder, on multiple occasions has contributed to the perception that the authority of science is under attack.[53]

[52] This is a quote from Robert Proctor, a historian of science. Mooney has had his eye on the relationship between politics and science since the early 2000s. His book, *The Republican War on Science* (2005), examines the Republican Party's stance on issues such as global warming, alternative medicine, and bioethics. In this work, he documents the systematic efforts of the Republican Party to undercut scientific authority by diminishing its influence on national policy. This text foreshadows the current (2019) moment in which the federal government is eliminating references to climate change on the Environmental Protection Agency's website, environmental protections are being rolled back, and the president has publicly vacillated on his trust of vaccines (Branswell, 2019). However, when the book was released, some reviewers dismissed Mooney's findings as polemical and not well-supported.

[53] Trump met with Andrew Wakefield during his 2016 campaign and invited Wakefield to his inaugural ball.

This is in stark contrast with the public goodwill biology enjoyed after Jonas Salk's development of the polio vaccine. While the lay public had concerns about physics and nuclear research after WWII, biology received immense support. The March of Dimes, which Roosevelt founded as the National Foundation for Infantile Paralysis in 1938, continued after WWII and attracted more positive attention after Salk's vaccine. In 1970, it began its annual walkathon, called the March for Babies, raising sufficient money to provide the initial grants for the Salk Institute as well as contribute to other research on infantile conditions. Whereas those who participated in these walkathons did so to raise money for research, those who walked in the March for Science did so to work against the silencing of science.[54]

A final difference between biology in the 1970s and the 2010s is that those who witnessed and participated in the atrocities of WWII are no longer the leaders of their fields. Many have died or retired. Those who were very young or not even born during the war did not experience the morality of scientific work the way the Salk Institute's founders did when they observed first-hand the testing of the atom bomb and the destruction of Nagasaki and Hiroshima. Younger scientists did not have to grapple with the morality of their choice of profession in the way Bronowski, Szilard, Crick, and others did. As the events of WWII retreated into the past, new concerns about science took precedence over the old. By the time the Berlin Wall fell in 1989, the Human Genome Project was gearing up and the biological sciences were taking advantage of the federal funding infrastructures of the Cold War. A new generation of biologists were at the forefront of their field and, while concerns about morality shaped their research, there was no longer the moral imperative to educate the public in the same way that Salk founder's felt compelled to do.

[54] The March for Science's hashtag as of 2019 is #sciencenotsilence.

While I have not used the word "revolution"[55] to describe any of the events I have described here, some of the historical actors I will discuss do. However, there is no reason to think that they mean it in the robust theoretical sense a science studies scholar would. Revolution for them seems to be a word they do not use thoughtfully. They may have used it to signal their belief that some technology would be significant in the ordinary course of their field's work. However, I would argue that there are similarities to an aspect of Kuhn's account of "revolution" that are relevant to my understanding of the Council's efforts. I would call the Council's efforts revolutionary in nature; however, the revolution failed.

When the Salk Institute established the Council, it happened in a time in which biologists felt compelled to do what STS has sought to do as a discipline, i.e. reflect on the power and morality of science within the context of society. People such as Salk and Bronowski believed that biology as a discipline could address social and ethical issues through its methods. This was a significant reimagining of the scope of the field and the meaning of ordinary biological practice. I contend that the institute's attempts to expand the purview and significance of biology was revolutionary. This drive to reconceptualize the field went against the forces that eventually took the Salk Institute over, as represented by Bourgeois's sinister portrayal of de Hoffmann or by Jacobs's depiction of him as a harried administrator who did everything he could to save the Institute. Either way, de Hoffmann's efforts caused the Institute and its members to: specialize, isolate, secure funding, and not take risks that would not be rewarded by traditional sources of funding for the biological sciences.

[55] Robert Sinsheimer has been associated with the so-called "biological revolution" which is used as a shorthand in the history of biology to refer to the turn to investigate phenomena at the molecular level, i.e. studying the relationship between DNA and proteins. Please see 2.5.1 for further discussion of Sinsheimer and the "biological revolution."

The Institute scientists did not give up, yet time marched on. Kuhn quotes Max Planck sadly reflecting on his own career saying, "a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and new generation grows up that is familiar with it" (1962/2012, p. 150). It follows that a scientific truth also fails if its proponents die before that new truth takes root. This new "truth" would have been a different way of doing biology as a practice and as a profession. However, the death of those who dreamed of making biology a more humanistic discipline that was intelligible to the public was significant. With their deaths came the end of the largescale efforts to transform the discipline. This was a failed attempt at conversion, which Kuhn defines saying: "conversions will occur a few at a time until, after the last holdouts have died, the whole profession will again be practicing under a single, but now different, paradigm" (1962/2012, p. 151). There was no conversion despite the efforts of the Council, but this does not mean that its attempts were not revolutionary in intent.

Kuhn's account of revolutions does not provide language to talk about failed revolutions or the effects of failed revolutions. His revolutions are dramatic, even if his historical fidelity is not quite as accurate as it could be. Robert Westman, a historian of science, provides a more nuanced articulation of how revolutions occur through the death and birth of generations, taking as his case Copernicus's heliocentric hypothesis (2011). This gradualist account resists Kuhn's interpretation that Copernicus's work with "revolution-making," something which Kuhn contends is common in science (Kuhn, 1957, p. 135). Westman shows that Copernicus's *De revolutionibus orbium coelestium* did not shake the foundations of astronomy overnight. It took until the second generation after Copernicus for the Catholic Church to regard his theory as a threat. This generation, described as activist in nature, used Copernicus's work for its own

purposes (Westman, 2011, p. 259). Some used it to support a Platonic ideology while trying to meet an Aristotelian ideal for demonstrative proof which Copernicus himself had avoided (Westman, 2011, p. 280). Later still, Galileo transformed Copernicus's work on planetary order into claims about how the heavens actually were, effectively challenging the authority of the Catholic Church (Westman, 2011, p. 510). Copernicus's writings were used as a framework for tackling problems, yet the generational circumstances in which they were taken up imparted to them a "revolutionary" quality, if one wants to call it that.

This account of the effects of Copernicus's work parallels the biologists of the 1970s failed attempts and how the consequences of their humanistic endeavors lingered and affected subsequent generations of biologists. While the Salk Institute was but one institute, their influence and networks spread around the world. The founders also had the shared experience with others of their generation of having survived WWII. It was the founders' experiences in WWII that made questions about morality and science relevant to their creation of the Salk Institute. Witnessing the consequences of unchecked scientific research and its weaponization gave the institute scientists and their peers reason to cede their authority over the future of human nature to the lay public. When the Council disbanded in 1974, its surviving members did not vanish. They continued to do research, mentor students, and attempt to involve the lay public in setting the agenda for future research. A notable example of this is the 1975 conference in Asilomar which produced public hearings that gave members of the lay public a say in NIH guidelines for genetically modifying organisms.

Robert Sinsheimer was a central convener of the 1975 Asilomar Conference in Pacific Grove, California. One of the purposes of this conference was for leading biologists to agree how to safely move forward with recombinant DNA technology. According to Sinsheimer, the

meeting was “a bunch of academics - focused, idealistic, and often naive - trying to do good, struggling to reconcile our conflicts, our apprehensions, our scientific ambitions our careers, our sometimes murky sense of obligation and emerge with a practical resolution” (Petsko, 2002, p. 1).[56] The conference attempted to respond to concerns members of the lay public had about the dangers of genetics research, specifically regarding the genetic modification of organisms. This meeting resulted in a series of resolutions that established guidelines for recombinant DNA experiments in collaboration with the lay public through open hearings.

Those who convened and attended the Asilomar conference either worked at the Salk Institute or were the professional peers of the institute scientists. These biologists shared the motivation to educate and inform the lay public. These attendees were luminaries in their field and subfields and went on to become leaders of the Human Genome Project. They were responsible for policy decisions for this initiative and allocated funding to labs that were involved in this international project.

When the next generation of scientists started and took over laboratories and the Asilomar attendees took over leadership of the NIH and DOE, the field had changed. Its members were facing a different global and technological landscape than that of the Salk Institute founders. However, the motivation behind the public outreach efforts of the 1970s continued to affect professional biology. In the 1990s, biologists shared their predecessors’ drive to improve the public welfare. As I will describe in the next chapter, the architects of the Human Genome Project, many of whom were at the Asilomar conference including Dulbecco and

[56] Biologists, such as Gregory Petsko note that biology of the early 2000s, the time in which he was writing, was different than that of the mid-1970s. However, he believed it was essential for biologists to respond to the newer concerns the lay public had about cloning, genetically modified food, and bioterrorism. He proposed an “Asilomar moment” was necessary to address these concerns which, significantly, were virtually identical to the ones raised as in the Cold Spring Harbor meeting.

Sinsheimer, intended for it to be the key to understanding and curing human diseases. The imperative to benefit the public through biological research which emerged in the 1970s can be seen in the Human Genome Project. But it did not survive in the form Bronowksi and Salk hoped it would. Specifically, the motivation to educate the lay public did not continue in earnest during the 1990s.

The subsequent chapters will investigate the communicative challenges biologists face currently. These chapters will answer the question: what, at the level of everyday practice, prevents biologists from conducting largescale public education initiatives? It will also show the material practices of Lab X's biomedical research reflect Bronowski's moral concerns. In doing so, the chapters will answer the question: what happened to the biological community's concerns about the morality of science that emerged in the 1970s? By focusing on the training of novice scientists, I reveal the difficulty of everyday biological practice. I also offer an answer to the question: where did biologists' focus on communicating the significance of their research go? The conclusion of this project tackles two interrelated programmatic concerns of STS: what can it mean to do a laboratory study now and what are ways an STS scholar can productively relate to science?

The answer to the last question is that which serves as a methodological guide for this project and takes its inspiration for Jonas Salk and Jacob Bronowski's desire for social scientists to work hand-in-hand with biologists to uncover the social and humanistic significance of science. My ultimate thoughts on the opportunities that the present moment offers to STS respond to Salk's vision for lab studies and Bronowksi's for the Council.

> "If the public could be helped to understand how scientific knowledge is generated and could understand it is comprehensible and no more extraordinary than any other field of endeavor, they would not expect more of scientists than they are capable of delivering, nor would they fear scientists as much as they do.

This would clarify not only the social position of scientists in society, but also the public understanding of the substance of science, of scientific pursuits and of the creation of scientific knowledge" (1979, p. 13).

Chapter 3

Model Organisms as Abstract Standards and Communicative Tools

3.1 Some Effects of the Human Genome Project

While the Human Genome Project affected much about the scale, organization, and focus of the biological sciences, I want to emphasize how it changed the models and techniques practitioners used. This is entirely because the members of Lab X spent most of their weekly meetings discussing issues related to their models and techniques. Additionally, their mouse models, and how they used them, became means by which the lab members communicated with the rest of their field. This chapter focuses on how Lab X developed a new mouse model of Down syndrome (DS) which they argued ought to be regarded as the "gold standard" for all mouse models in DS research. This was one of the few times while I was in the lab that the members were explicitly concerned with communicating with the rest of their field. While they worked within a loosely defined area that focused on cognition associated with DS, they occupied several other sub-domains of research as well.[57] However, the differences between labs working on cognition associated with DS can be significant. For example, some labs may work with non-genetic mouse models or work with ones that have significantly different genomes. Lab

[57] For example, they also contribute to research on Alzheimer's disease, but use DS genetic models to do so.

X's work developing a new mouse model that it intended to set the standard for *all* of DS research is a large goal and one that could bridge the communicative gaps within this field.

Before discussing the lab's new mouse model, how they developed it, and the obstacles they encountered trying to establish it as a standard, I will first give some historical background on experimental organisms as they relate to Lab X's work. Specifically, I will convey what counts as a "model" organism for this group of biologists.

Lab X is explicit in its belief that a model organism is not just any animal or organism used in scientific experimentation, and the historical literature on this topic agrees. "Model organism" is a relatively new phrase that started appearing regularly in the 1960s and 1970s. The "model" modifier distinguishes a class within the more generic "experimental animal" or "experimental organism." Fields of biology have used animals in experiments for centuries, as is documented in historical accounts such as Karen Rader's work on mice, which traces the selective breeding for traits to the centuries-old practices of mouse "fanciers" (Rader 2004, p.10, 32).[58] Rachel Ankeny and Sabina Leonelli explain that an experimental animal differs from a model organism because even though an experimental animal can stand in for another organism or specific biological process in one, an experimental animal is not *standardized,* whereas a model organism has undergone a social and material process of standardization (Ankeny and Leonelli 2011, p. 315-318). Furthermore, it has been standardized in a way that the community in which it is embedded regards as exemplary. In this way, the "model" in model organism, picks it out as being exemplary in some way. For an organism to be considered "exemplary" in some way it must meet a high standard, not as an individual, but as a population.

[58] For example, Carrie Friese and Adele Clarke (2012) look at primate models in reproductive science in the early 20th century. Frederic Holmes (1993) explores the use of the frog in experimental physiology starting in the 1600s.

One way for an organism to meet the high requirement of standardization, and thereby become a model organism, is for it to have its genome sequenced, or at least partially sequenced and on its way to completion. This is the case for Lab X and other biomedical labs. As Ankeny and Leonelli note, there is no explicitly established requirement that a model organism have a detailed genetic account for it to be considered standardized; however, this is the most common way in which they are standardized. Furthermore, the decreasing cost of genetic work and the relative abundance of standardized organisms has given rise to more biological work being grounded in genetics (see Rheinberger 1997). Additionally, as I will discuss later, genetics has become foundational to the field of biology, so being standardized in this way gives the organisms extra epistemic weight.

Lab X is also quick to explain that the story of the term "model organism" is bound up in the history of advances in molecular biology and genetics. In fact, the phrase "model organism" only became used commonly used in publications in the biological fields in the 1980s and in the context of work on genetic sequencing (Ankeny and Leonelli 2011, p. 313). However, the term began to emerge with increasing regularity starting in the 1960s, due to the development of the field of molecular biology and continuing into the 1970s with early work on DNA mapping (Ankeny 2010, p. 93; Ankeny and Leonelli 2011, p. 314; Gilbert 2009 p. 53).[59] In the 1990s, there was a metaphorical explosion of biological publications using the term, which coincided with the large number of genome sequencing projects of non-human organisms. At the same time, the Human Genome project was underway (Ankeny, p. 94; Ankeny and Leonelli 2011, p,

[59] Hamilton Smith, Thomas Kelly, and Kent Wilcox isolated and characterized the first "type II" restriction enzyme in 1970, which proved extremely useful for showing that mapping DNA was possible. "*Hin*dII" is a restriction nuclease that Smith, Kelly, and Wilcox showed would always cut DNA after a sequence of six specific nucleotides. Type II restriction enzymes were better for the laboratory setting than Type I restriction enzymes because they cut nucleotide strands at invariable short lengths (4-8) and had one function, as opposed to the multiple functions of Type I kinds. The single and stable function of Type II restriction enzymes made it perfect for laboratory work and that would later be used to understand later manipulate DNA sequences. (*See* Smith and Welcox 1970).

313). The gene sequencing projects of non-human animals and the Human Genome project were not unrelated. The hope was that by studying non-human animals, biologists would be able to identify genes responsible for certain phenomena that could be mapped on to humans. It was against this background, and in the expectation that gene sequencing would yield powerful inferences and explanations, that the notion of a model organism entered circulation in biology with the connotation that they are genetic models.

In anticipation of a trove of data expected to come out of the individual instantiations of the Human Genome project, funded by the National Institute of Health, a canon of "model organisms" were approved by the NIH and the Department of Education (Collins and Galas 1993, p. 43; see also Collins et al. 1998). These organisms were *Caenorhabditis elegans* (*C. elegans*), a nematode worm, *Drosophila melanogaster* (*drosophila*), the fruit fly, *Escherichia coli* (*E. coli*), a bacterium, *Saccharomyces cerevisiae* (*S. cerevisiae*), yeast, and "the mouse," (officially called *Mus musculus*) which was considered "the best mammalian model for studies of a broad array of *biomedical* research questions" (Collins et al. 1998, italics added). These five organisms were, in the context of the work being done to sequence their genomes, intended to serve as general models of the human genome. Since then, more organisms have been approved by the NIH as specifically *genetic* model organisms because their genomes have been sequenced. These include: *D. discoideum*, a soil-living amoeba; *S. pombe*, "fission yeast;" *C. reinhardtii*, single-cell green alga; *Tetrahymena* species, a versatile protozoon, "EHUX," a photosynthetic plankton; *Arabidopsis thaliana*, a flowering plant; *Physcomitrella patens*, a moss; the zebrafish; the mummichog, a killifish; a turquoise African ruvuline; the Carolina anole, an arboreal lizard; and the African clawed frog. The organisms chosen for the Human Genome projects were among the most commonly used systems in the biological sciences at the time and continue to be. The

subsequent, specifically genetic model organisms were all added to NIH's list of model organisms after 2002.

During and after the Human Genome Project, research communities grew up around particular model organisms, such as the mouse, the worm, and the fly. Practitioners began to identify themselves as worm biologists, fly biologists, or biologists tied to another model organism. This in part was due to the specific techniques they used to work with their particular genetic model. Their identities as biologists of a particular model organism also stemmed from the model-specific data they produced that was not readily applicable to other organisms. As time passed, particular model organism communities became focused on particular kinds of problems and questions (Leonelli, 2007). For example, biologists working with *Arabidopsis* became involved in studying basic genetics and *C. elegans* workers studied behavior of single cells and development. Additionally, separate databases emerged to store and share information about particular organisms such as: FlyBase, WormBase, and The Arabidopsis Information Resource (Leonelli, 2007). The socio-material divisions within the biological sciences after the Human Genome Project created communicative gaps between communities which were ultimately interested in similar topics surrounding the relationship between genetics and cellular behavior.

Laboratories such as Lab X represent an ongoing phase in contemporary biomedical research in which biologists are not just defined by the kind of model organism they use, e.g. "mouse biologists" or "worm biologists." Instead, they now define themselves by the line of a particular model organism they use. Within the research communities that focus on age-related neurodegeneration and cognition, Lab X is one of the labs which defines itself as using "trisomic" or DS mice. In DS research, Lab X has historically defined itself as a primarily

"Ts65Dn mouse" lab, which is one mouse line out of the many trisomic mouse lines used currently in DS research. While there is a much bigger social, material, and communicative gap between mouse and worm biologists, what concerned Lab X more was the gap between the biologists within the same model organism community who operated within the subfield of DS research.

3.2 Introduction to the Rest of the Chapter

This chapter is ultimately a story about Lab X and the new complete genetic mouse model of Down syndrome they had developed. They have argued in print, and amongst each other, that this mouse should be used in all genetic research on DS as the "gold standard." In particular, this mouse should be used instead of the most popular mouse model (i.e. the Ts65Dn), which they claim is inferior to their new mouse. The catch is, they are unable to use the mouse they developed and have resorted to using the mouse they have deemed to be inferior. Additionally, in the year following the publication of their paper promoting the superiority of their new mouse, they spent substantial lab resources using the older "inferior" mouse in ways that provided no explanation of any aspect of DS. I will show in this chapter that the lab resolved this problem and justified their work with the "inferior" mouse in an epistemically sophisticated way. By discussing how the lab did this, I will also illuminate how, in practice, model organisms can serve as abstract standards for scientific work that impact the epistemic value of scientific claims, regulate practice, and constrain future work. My goal here is *not* to evaluate whether the lab is correct in their determination that the new mouse is the best model for DS research, nor is it to critique the standards which were operant in their determination.

Instead, my motivation here is to uncover *how* the lab members set their new mouse as a standard and how this affected their subsequent practices.

This case comes out my ethnographic work as well as analyses I have done on the lab's publications and manuscript drafts. [60] Here, I focus on issues which are of interest to philosophers of science with a practice focus, namely regarding the norms of actual scientific practice (Rouse, 1996; Chang, 2011; Andersen & Wagenknecht, 2012) and the epistemological functions of model organisms. My guiding questions are: How does the lab justify working with what they believe to be an inferior mouse model? Additionally, how does their new mouse line advance their goal of understanding DS in humans and how does it guide their future work? I engage with philosophical literature here because the nature of Lab X's concerns about standard-setting and justification are best supported by work within the philosophy of science. Furthermore, in developing an analysis of how Lab X set their new mouse as a standard, and what this reveals about their hierarchy of normativity, I work at the epistemic level of analysis to offer an account supported by, but not reliant, on the specific language of the practitioners. To remain faithful to the analytical rigor of Lab X, I draw on literature that upholds a similar modernist commitment to rationality. In this way, I have let the unique order of my site inform my analysis. However, by answering the above questions, I intend to: 1) demonstrate the value of ethnographic methods to the philosophy of science for revealing dimensions of practice which are not apparent in publication; b) show how an analysis informed by the style of reasoning of a particular site illuminates how that reasoning is born out in that site's practice.

[60] Even though the lab I will be discussing focuses on the neurobiology of cognition in DS, the research community has other interests which include: the cardiovascular system, comorbidity, the endocrine system, neuronal pathways, neurotransmitter restoration, drug discovery, sleep, nutrition supplementation, cancer risk, and fertility.

To provide an answer to these questions, I will examine how Lab X itself has sought to justify (in print and in person) the use of the older, inferior model. The way in which Lab X does this may be surprising. The lab argues that the old mouse model *is*, in some respects, a suitable model – precisely because (they argue) in some respects the old model can be shown to be functionally equivalent, in a limited sense, with the new model. In the eyes of Lab X, this somewhat convoluted strategy of asserting their new complete genetic model of Down syndrome should be regarded as a field-wide standard and meeting it indirectly with an "inferior" mouse is justifiable. They regard it as justifiable because they have shown that the intracellular behavior of one protein in the inferior mouse is functionally equivalent with that in their new mouse. This allows them to claim that, for the purposes of their work, they have met the new high standards constructed through their new mouse line. However, by doing the work to demonstrate the limited functional equivalency between the two lines, the lab has also reaped several epistemic benefits: i) by doing so, they have afforded the inferior mouse model equivalent epistemic weight; ii) they have established a procedure which other labs could use to overcome the same problem, iii) they have made the new mouse a standard against which all DS mice can be evaluated; iv) the lab has designated what they believe to be the necessary context in which the best and strongest explanations of DS must occur as well as the terms in which these explanations must be.

Before providing the details of the case, I will first (3.3) discuss the methodology I use in this chapter as well as my site. Second (3.4), I will provide a brief review of the literature on model organisms and practice-oriented philosophy of science. (3.5), Third, I will provide data from my field notes, interviews and Lab X's published paper concerning the new mouse as a standard-setter and how the lab is trying to meet those standards. Fourth (3.6), I will answer two

questions: (3.6.1) How does the lab justify working with what they believe to be an inferior mouse model?; (3.6.2) how does their new mouse line advance their goal of understanding Down syndrome in humans and how does it guide their future work?

3.3 Model Organisms and Practice-Oriented Philosophy of Science

Model organisms that are intended to serve as genetic representations of their targets are a relatively new feature of the biological sciences. The practitioners pursuing humanistic and social scientific studies of science have taken note of this phenomenon and have inquired into how these particular kinds of models are produced and how they figure into scientific practice, including explanatory practices. The community of researchers working on these topics is an interdisciplinary one comprising philosophers of science, STS scholars, and historians of science. My case of the "Genetically Correct Down Syndrome" (GCDS) mouse is similar in its aims to illuminate how model organisms function in practice and how they are involved in the construction of explanations. However, this case presents a less tidy story of how a particular line of a model organism was developed and how it serves the function of being an epistemological constraint and standard for current and future work. This is not to minimize the value of the literature on model organisms, but to illuminate the philosophical payoffs for employing ethnographic methods to delve into the less straightforward reality of everyday scientific practice. In order to show how ethnographic approaches in the philosophy of science can be of value, I will situate it in the context of several foci of practitioners interested in scientific practice.

Notably, the philosophical literature on model organisms seeks to provide practice-friendly accounts of model organisms that are applicable to my case. The literature is in agreement that a successful model, including model organisms, must have the capacity to serve as an "indirect representation of the world" in some relevant way (Giere, 1988/2010, pp. 82; Godfrey-Smith, 2006, pp. 726).[61] This definition leaves debatable what standard a model should meet in order to be the *best* and allows a modeler's own standards to be taken into consideration. This does leave room for critical work on how extrapolation ought to work when there are significant differences between model and target (Steel, 2007, pp. 86). However, it would be a challenge to arrive at a general principle for what counts as a good model organism and successful extrapolation.[62] In the literature on model organisms, there is a move away from trying to arrive at an overarching principle of success for all organismic models in biology. Instead, philosophers have taken case-based approaches to discussing what standards determine the *best* model organism. There is some agreement that the questions practitioners are pursuing in the context of their given fields determine the standards for what counts as the best model (Burian, 1993, pp. 360; Bolker, 1995, pp. 451; Ankeny & Leonelli, 2011, pp. 314). In approaching the case of the GCDS mouse, I do not seek to provide any critique of the Lab X's standards (in particular that of the genetic "gold standard"), but join the practitioners focused on uncovering the modeler's own standards and how they operate in biological practice.

Scholars in STS and the history of science have also taken a case-based approach to model organisms. They have also focused on how scientists chose and standardized them as well

[61] For discussions focused on how model organisms represent targets through phylogeny or developmentally related cells, see: (Ankeny 2001; Weber, 2004; Leonelli 2007; Ankeny & Leonelli 2011).
[62] As Tudor Baetu has shown, there are many different kinds of models in contemporary biology that serve multiple functions and are evaluated by different standards. To complicate things further practitioners use multiple models in coordination to meet particular scientific aims (Baetu, 2014).

as the social and cultural practices surrounding their use. Although the case of the GCDS mouse does not include discussion of the greater social and cultural factors involved in the line's development, it pursues STS's and the history of science's goal of telling the story of the development of a particular model. For example, Karen Rader traced the history of *mus musculus* (aka. The "Wild Type" or WT mouse) focusing on how biologists standardized it (2004). Other historical works in STS have similarly shown how scientists developed other organisms focusing on their socio-pragmatic justification for doing so (Kohler, 1994; Creager, 2002).[63] Yet, the story of the GCDS mouse is less straightforward perhaps because it does not have the vantage point of the historian. It will take decades before one could determine how the GCDS mouse has affected, and will affect, DS research. I will show, however, that there is value in determining the intentions of Lab X and the standards they have set with their mouse prior to the clarity a future historical analysis could provide.

I would also argue that participant-observation ethnography is suitable for discovering epistemic features of modeling practice and not at odds with current practice-oriented trends in the philosophy of science. One group that has inquired into what scientists actually do and, in particular, how explanation works in biological practice are the New Mechanists (See Bechtel & Abrahamsen, 2005; Craver 2007; Craver & Darden, 2013). This research program moved away from viewing explanations as "subsumption of phenomena to be explained under a theory or law" (Bechtel & Richardson, 1993/2010, pp. xvii) Instead, the New Mechanists have looked at how biologists give and epistemically value "mechanistic" explanations and have used this to

[63] See Also Carrie Friese and Adele Clarke's work on human reproductive sciences (2012) as well as Nicole Nelson's work on how scientists make inferences using animal models (2013).

guide their work.[64] In their seminal paper, Machamer, Darden, and Crave strongly state that the biological concept of "mechanism" is "central to an adequate philosophical understanding of the biological sciences" (Machamer, Darden, & Craver, 2000, pp. 3) This paper is in the same spirit of looking to actual practice to determine what is necessary for a philosophical understanding of aspects of the biological sciences. Although the case of the GCDS mouse is not an instance of explanation, Lab X is explicit, as I will show in §5, that their aim is to be able to use their mouse models to ultimately find and explain the mechanisms involved in DS.

The philosophy of science has not only developed interest in the topic of practice, but has incorporated a variety of methods to uncover what scientists are doing in their everyday work. William Bechtel's WORking Group on Diagrams in Science (WORGODS) studied how circadian biologists used diagrams in practice, especially how graphical representations can explain biological mechanisms. Some members used archival methodology to analyze drafts of diagrams to understand how scientists construct diagrams (Abrahamsen & Bechtel, 2015; Sheredos & Bechtel, 2016; Sheredos & Bechtel, 2017). One paper that came out of this study illuminated the endogenous norms regulating graphical practice, drawing an important distinction between ideal and non-ideal normativity on which I will be drawing (Sheredos, 2017). Other philosophers have undertaken collaborations with scientists employing philosophical analyses to aid in revealing new dimensions in the scientific work itself (Woody, 2004; Bursten et al., 2016; Bursten, Hartmann, & Millstone, 2016). There have been notable instances where philosophers have used ethnographic methods to engage with philosophical problems. Strong examples of this are Miles MacLeod and Nancy Nersessian (and their

[64] The New Mechanistic movement has produced a diverse body of literature and my treatment here does little justice to it. I am making note of it here as a way of demonstrating the current practice-focused currents within the philosophy of science that give support to employing ethnographic methods.

collaborators), who have specifically investigated modeling practices (MacLeod & Nersessian, 2013) and have shown the non-explanatory value of models in systems biology (MacLeod & Nersessian 2015). Like MacLeod and Nersessian's work, the case I present here of the GCDS mouse is not a means of contradicting the value of the more critical projects in the philosophy of science (*Id.*, pp. 11). Instead, by complicating the accounts of model organisms and pre-explanatory scientific work, I aim to show the untapped epistemic richness of scientific practice.

3.4 A Philosophical Approach to Ethnography

Even though ethnography is not a traditionally philosophical method, there is precedent for using it in the philosophy of science (discussed in §2). I use it because if we take seriously the philosophers who call for a turn to look at actual scientific practices (Ankeny, et al., 2011) we need to adopt methods that offer a way of studying practices as they occur, even if it means drawing on the tools of the social sciences. However, as I will show, we need not sacrifice the values and focuses of philosophy of science.

The unique value and role of the new mouse model emerged through the course of this study against a backdrop of more high profile published papers, grants, collaborations, and experiments. Of the 22 papers the lab published during the 2015-2016 academic year, only one had the new mouse as its focus. However, the frequency with which the lab members brought it up in lab meetings (often in relation to other projects that were *prima facie* unrelated) gave me cause to investigate the significance of their new mouse line. Throughout my participation in the lab, I followed up on the new mouse through more focused interviews and examinations of publications.

I chose the published work to analyze by looking for references to the GCDS mouse in the DS literature. I also followed three experiments from conception to publication which members told me was a way of establishing that a certain protein (APP) functioned the same way in the "inferior" mouse as well is their new one. Although much of the evidence I discuss below comes from the Lab's published work, my interpretation of the published work often goes beyond what was stated explicitly in-press, and my interpretation was supported by unstructured interviews and discussions with lab members. Unlike other laboratory studies which focus on reconstructing a particular lab culture from the ground up, my investigation was guided by the lab members' epistemological concerns regarding setting and meeting a new high standard. In this way, my methods are more closely aligned with ethnomethodology, which is concerned with analyzing moments of interaction to determine the "rational properties" of people's actions and their sense-making practices (Garfinkel, 1967, pp. 10). However, unlike ethnomethodology, I did not confine myself only to talk-in-interaction nor to explicating the norms of success, for example, in the terms that lab members themselves would use (Boden & Zimmerman, 1990; see also Psathas, 1995). Rather, I aimed to work at the epistemic level of philosophical analysis regarding scientific practice (Weisberg, 2013, pp. 19).[65] Working at the epistemic level, one asks "what categories (or language more generally) does one need to provide philosophically adequate understanding of practice?" These may not be the scientists' own categories and accounts. Lab X's practices, categories and accounts further *their* aims studying the genetic basis of human DS. My aim is to understand the epistemological functions of model organisms and how they can serve as epistemic standards or constraints in practice. This is a philosophical

[65] See Weisberg (2013) for his explanation of philosophical theorizing at the epistemic level, a term which he attributes to Stacy Friend's unpublished 2009 comments.

project which necessitates developing philosophical categories of analysis which can be applied to the scientific practice at hand.

A philosophical account at the epistemic level has two payoffs in the case I will present. First, it captures how members of Lab X used the new mouse model to address epistemic issues regarding how a model can establish a standard and how a model can inform how that standard ought to be met. Second it can productively enrich our understanding of model organisms and standards in practice.

3.5 Methodology and Field Site

In the course of my time in Lab X, I became interested in how its members were dealing with the puzzle of championing a new mouse as the best mouse for DS research, while not actually using it, but still regarding themselves, and being regarded, as successful.[66] I take my methodological inspiration from others who have conducted laboratory studies that focus on everyday scientific activity and employ detailed analysis of these practices (e.g. Lynch & Woolgar, 1990; Lynch, 1997; Alač, 2011; Alač and Hutchins, 2004). However, I do not take much inspiration from laboratory studies which intentionally take the "stranger's" perspective, i.e. an ethnographic perspective which precludes the researcher from regarding any lab work or scientific knowledge as familiar or as a means for interpreting lab practices (e.g. Latour &

[66] My evidence for their research community as regarding them as successful is threefold: 1) My interactions with other labs and members of their research community; 2) Funding agencies continue to award Lab X grants which tout their new mouse as being one of their accomplishments. These funding bodies include, NIH, The Jerome Lejeune Foundation, Cure Alzheimer's Foundation, LuMind/RDS Foundation, Alzheimer's Association, Larry L. Hillblom Foundation, and others; 3) In the past two years, the lab has published over 20 papers in leading journals of their field including *Neuron, Neurobiology of Disease, The Lancet Neurology, Alzheimer's & Dementia* with favorable external citations.

Woolgar 1983). Instead, I rely on my familiarity with biology and the accumulation of experience and knowledge I have due to the amount of time I have spent in Lab X as a guest and participant-observer. To put it in another way, I rely on the unique adequacy I have developed in the kind of neurobiology Lab X does and how its members do it as well as the empathetic validity I attained due to my relationships with them.

In my presentation of the case, I will be discussing a single paper that the lab published on their new mouse and their motivations for doing so. I will be drawing entirely from my ethnographic data (audio and field notes) to inform my analysis of this paper and to describe their everyday work and motivations; however, I will only provide a citation when I am directly quoting a lab member. I also will be drawing on publications in the field of DS research that demonstrate the field's evaluation of the new mouse in order to illuminate the significance of Lab X's conviction in the new standard they have produced.

In all of its work, Lab X focuses on the signaling of neurotrophic factors and their role in intracellular actions.[67] The researchers' hypothesis is that the neurodegeneration that occurs in age-related disorders, including DS, results from a genetic predisposition to dysfunctional intra-cellular signaling mechanisms which cause an overexpression of certain proteins, such as amyloid precursor protein (APP) and its substrate amyloid beta (Aβ).[68] Like many researchers in the field (Salehi, 2006), Lab X believes that APP is responsible for the cognitive effects of conditions such as DS and specifically thinks that successful models of these kinds of

[67] Neurotrophic factors are proteins which influence the developing brain (e.g. neuron specification or "cell fate," cell body migration, axon pathfinding, synaptogenesis, etc.)

[68] Although DS is not typically regarded as age-related, the neurodegeneration that occurs in DS *is* age-related and occurs between ages 40-60 in up to 70% of individuals (Malt, et al., 2013). Because Lab X is focused on cognition and reduces cognition to neuronal processes, they include DS among the conditions that are more obviously age-related.

pathologies must correctly model this protein's behavior above all else.[69] Furthermore, because this condition is a genetic order, the lab works to offer explanations grounded in genetics through using models that (in some sense ideally) represent the genetics of the condition in humans.

During my observation, the Lab worked with eight distinct lines of mice which are modifications of the ubiquitous "wild type" mouse. All of these lines are accepted in DS research as having the capacity to serve as genetic models of different aspects of DS in humans. Here I focus on the lab's new mouse which is the only existing mouse line that is a complete genetic model of human DS. I will call it the "GCDS" mouse, which stands for "genetically correct Down syndrome" mouse which, they argued in publication, should be regarded as the gold standard of mice in DS research. [70] In human DS, there is an extra, third, copy of Human Chromosome 21 (HSA 21), which results in an extra copy of all the genes on that chromosome. In mice, the homologous genes are scattered across three mouse chromosomes: MMU 10, 16, and 17. [71] In all the non-GCDS mouse lines, what researchers have done is to duplicate some portions of these chromosomes, targeting a few mouse genes which are homologous to parts of HSA 21. For example, one popular mouse line, the Ts65Dn (which I previously mentioned as the "older inferior" mouse line), has extra copies of regions of the MMU 16 chromosome only: the Ts65Dn mouse is not a complete genetic model of DS, since only some of the genes which are triplicated in human DS are triplicated in the mouse line. Likewise, all other non-GCDS mouse lines exhibit only partial genetic fidelity to Human DS. The GCDS mouse line was developed

[69] APP is a highly conserved protein, meaning that it is present in many organisms and has been maintained by evolution despite phylogenetic changes. However, what APP does is not completely understood, yet there is agreement in the neuroscience community that it is involved in maintaining healthy brain functions.
[70] This is not how the lab refers to their new mouse; however, I am anonymizing the mouse to protect the identity of the lab. But significantly, the lab has referred to this mouse in print as being a "genetically correct" model of DS, hence I call it the "Genetically Correct Down Syndrome" mouse because it reflects their stance on the mouse. It also has the added bonus of being as bold as the actual name of the mouse line.
[71] The models of DS used in Lab X are: the Wild Type mouse, Ts65DN, Ts1Cje, Ts1Rhr, Dp(10)1Yey, Dp(16)1Yey, Ts1Yah, and their new "GCDS" mouse (anonymized to protect Lab X).

specifically to provide a complete genetic model. The GCDS mouse is unique because it has extra copies of all (and only) the mouse genes on these three chromosomes which are homologous to the genes on HSA 21. For Lab X, the genetic correctness and completeness of the mouse makes it the superior model.

3.6 Using the GCDS Mouse

From my fieldwork and analysis of their written work, I determined that Lab X's goal is to create and work with a mouse model that is a complete genetic model of human DS.[72] Much work in DS research involves using several different kinds of mouse lines in order to make a particular claim.[73] Lab X has, like many other labs, used several partial mouse models of DS and constructed through publication a complete genetic model. By this I mean that labs in this field write papers which rely on data from different mouse chromosomes across several different mouse lines. By combining all the data across these different mice and chromosomes, they are able to construct on the page a complete genetic mouse model, which does not concretely exist, to account for a given phenomenon. From participating in discussions and conducting interviews with them, members of Lab X do not view this as an acceptable ideal to guide their research. Lab X would prefer to work with a single complete genetic model.

[72] This was reflected not only the amount of time and resources the lab spent used to acquire and promote this mouse, but also through Lab X's publication championing the virtues of their new mouse. In this paper they state, "The role of the genetic background in expression of DS phenotypes in mouse models is evident and should be further examined in future studies. The stage is now set to more effectively discover and decipher DS-relevant phenotypes in genetic models of DS, and the[GCDS] mouse can serve to simplify and focus these studies" (Lab X in print, 2015). This was also made clear when I asked lab members why they are not using the GCDS mouse in an experiment, as I say elsewhere in this chapter, the lab director said, "Well I think we should work with the [GCDS], I think everyone should, but we can't."

[73] See Torre et al., 2014 as an example.

This was made explicit in a planning meeting in February 2016, which was after their publication promoting the GCDS mouse. In this meeting there was a discussion between a senior scientist and an advanced graduate student regarding whether it was necessary to go to the lengths they were going to establish the GCDS mouse is an exemplary model. The senior scientist explained that "All Down syndrome mouse models have to be compared to the [GCDS]." When the graduate student asked why, the senior scientist elaborated that because the other mouse lines produced phenotypes attributed to DS, but were not robust genetic models, there was a need for such a genetic model. Furthermore, sharing the mouse with other researchers would be beneficial because it would "involve the [DS research] community and produce a lot of phenotype work" for other labs wanting to establish genotype/phenotype relationships. The DS research community has been aware that although they have produced strong phenotypic models with partial fidelity to human DS, they have, so far, lacked a complete genetic model that they could use to determine what genetic variances are responsible for particular phenotypes. In order to rectify this, other researchers have previously attempted to create complete mouse models of human DS. Lab X was similarly motivated to create the GCDS mouse; however, it was not the first publicized attempt at such a model.

The earliest mouse model that DS researchers offered as a complete genetic model was the Tc1 mouse. Yet practitioners in Lab X believe their new GCDS mouse line surpasses the Tc1 as a superior genetic model. The Tc1 mouse model contains two mouse chromosomes with an extra *human* chromosome (HSA 21). In this mouse, the biologists manipulated mouse embryonic stem cells to produce and transmit almost complete HSA 21 in order to serve as a model of human DS (O'doherty et al., 2005). The Tc1 was initially regarded as being a model of "an almost complete human chromosome" in a mouse (O'Doherty et al., 2005). However, as Lab X

and others have pointed out, the Tc1 mouse did not meet the expectations of the DS research community. In their publication, Lab X noted that the human genetic material in the Tc1 had multiple and significant structural changes. This included six duplications, 25 structural rearrangements that are not present in human DS, and a large deletion. Furthermore, only approximately 50% of the neurons in these mice contained the human genetic material (Lab X in print, 2015).[74] This makes it difficult to make justifiable claims about DS in humans using the Tc1 mouse: it is always possible that the erroneous changes to the DNA are responsible for any observed phenomenon.

What has been most problematic is the fact that not all of the neurons in this line contain the human DNA (Gupta et al., 2016, pp. 545). This is because it presents problems for behavioral testing as well as experiments on the neurons themselves, because in both cases the cause of the observed phenomena would be unclear – a result could be explained by the unaffected mouse neurons, the ones with human DNA, or an interaction between these two kinds of neurons.

For Lab X, the GCDS mouse is a possible solution to the problems of the Tc1. In their paper, they note that the GCDS mouse differs from the Tc1 because *all* the neurons have a triplication of *native mouse genes* (not transplanted human ones) which are strongly believed to be homologous to those on HSA 21. These triplications are of the mouse's own genes, eliminating the concern over the effects of adding human DNA to a mouse neuron. Lab X developed the GCDS mouse which contains an extra copy of all of the regions of MMU 10, 16, and 17 that the DS research community considers to be homologous to HSA 21. The lab sees this

[74] To protect the identity current members of Lab X the best I can when analyzing a readily available paper of theirs, I am not providing a citation to their paper. I am also paraphrasing their findings here so as to minimize the risk of discovering the identity of the lab through use of search engines.

mouse as standard-setting in their field because of its genetic completeness and accuracy to human DS. They argue,

> "This 'triple trisomic' [GCDS] model represents the most complete and accurate murine model currently available for experimental studies of genotype-phenotype relationships in DS" (Lab X in print, July 2015).[75]

In addition to serving as a more precise model of human DS, the possibility of working exclusively with the GCDS mouse ideally has practical payoffs for Lab X. Keeping colonies of eight mouse lines is expensive, time consuming, and has often caused the "mouse person," "Monica"[76], to be away from the lab and in the vivarium, which is not housed in Lab X's research space. Monica is a skilled and experienced lab technician who has a talent for training the lab's graduate students, so her necessary absence from the lab space has slowed down the rate at which the lab can do experiments. Even though the lab has tried to offset this problem by having graduate students take more responsibility for the mice with which they are working, the lab director knows that the GCDS mouse could free up Monica's time. He has joked, "As soon as we get enough of them, you could go on vacation [Monica]! Who knows what you could do with all that extra time" (Lab Director in meeting, October 2015).

Despite how promising the GCDS mouse is as a genetically complete model of DS and the practical benefits it could have for Lab X, the lab members rarely use this mouse. In an interview with the lab director, I asked why this was the case and he gave me several practical reasons. First, each mouse costs about $15,000 and must be purchased from the sole breeding facility on the east coast of the United States, with whom they collaborated in making this mouse. Second, the life expectancy of these mice is quite short: eight months is considered

[75] Again, I am not providing a citation to their paper so as to protect the identity of the lab. I have included a quote from the paper here it is not a search query that produces the paper as one of its results.
[76] Pseudonym to protect identity.

advanced old age for GCDS mice, whereas the regular Wild Type (WT) mouse line has a life expectancy of 1.5-2 years. For a lab that wants to study age-related cognitive degeneration as it occurs, it is almost useless to get an old mouse that has already undergone the changes which they hope to study. Third, the males are aggressive and need to be isolated from each other, making their care more expensive.[77] Fourth, there is only about an 11% chance of successfully breeding one of these mice. The DS research community has noticed the fourth limitation of the GCDS mouse and has noted that the time and effort required breeding these mice coupled with the low rate for successful breeding causes this model to be ultimately impractical:

> "This breeding is time consuming and expensive. Two generations of breeding are required to obtain each mouse and the final yields are much lower than expected….For preclinical evaluations with behavioral testing or other analyses where it is desirable to have a dozen or more age- and sex-matched individuals, with and without drug treatment, generating sufficient numbers becomes impractical for most researchers, and certainly for extensive screening of potential drug treatments. This is likely reflected in the appearance of only two publications using the [GCDS] mice." (Gupta et al., 2016, pp. 549).

While the field is in favor of a genetically complete model and Gupta et al. considered the GCDS mouse important enough to receive considerable attention in their review, the practical problems make it unusable as a regular feature in DS work.

In addition to the practical problems this mouse poses, using it also involves theoretical obstacles: the GCDS mouse deviates from the current standards for "good" DS mouse models. Down syndrome researchers, particularly those working on cognition, have chosen to work with mice that have strong cognitive phenotypes. A "good" mouse model has decreased performance in learning and memory tasks. This is, in part, because a strong deviation from the behavior of the wild type mouse has enabled researchers to draw connection between the genetic changes in

[77] Sharon and the lab manager had also mentioned the aggression of the mouse line to me about this within the first month of my participation in the lab.

DS and what they regard as cognitive deficits (Reeves et al., 1995). This is exemplified by the frequent use of the phenotypically strong Ts65Dn mouse, which practitioners have also regarded it as the "best" model of DS (Belichenko, 2004). When I distinguish the Ts65Dn as being a phenotypically strong mouse line, I mean that their performance in learning and memory task is regarded as having high fidelity to how human DS patients perform in comparable tasks (Davisson, Schmidt, and Akeson, 1990). However, a mouse line being phenotypically strong is often times distinct from a line having high genetic fidelity to what is known about human DS at the genetic level. As I discussed earlier, the Ts65Dn only has an extra copy of one of the three mouse chromosomes that are homologous to the entirety of human chromosome 21. The mouse also has copies of extra genes that are not on HSA 21, which has caused some worries regarding whether the strong phenotype that is present in this mouse is actually a result of unintentionally triplicated genes that are not homologous to those involved in human DS.

The GCDS mouse is a good example of how phenotypic performance and genetics can come apart. On the one hand, the GCDS mouse is genetically homologous to human DS to a degree which no other DS mouse can meet. However, the GCDS mouse performs almost as well as the wild type mouse on the usual learning and memory tasks, which makes it a bad phenotypic model. Lab X argues that even though there are better phenotypic mouse models than the GCDS mouse, because it is the most faithful genetic model, it should be regarded as superior. Lab X goes as far as to imply that the commonly used Ts65Dn mouse is inadequate for DS research by posing the rhetorical question,

> "Which [model] should be considered as more adequate – models with stronger phenotypes (e.g., Ts65Dn mice) or models most closely replicating genetic changes observed in DS (e.g. [GCDS] mice)? We view the genetic correctness as the most important feature for a genetic model. As such, we point to [GCDS] mice as a new standard by which to compare and guide studies defining genotype-phenotype relationships in DS" (Lab X in print, July 2015).

Through their 2015 paper, Lab X has gone on record saying that they regard GCDS mice as being *the* standard for DS research. However, as I have said, the lab very rarely uses this mouse. In the 2015-2016 academic year, the lab was only able to acquire five GCDS mice, three of which were gifts from the collaborating lab. Five mice are not enough for Lab X to produce enough experimental data. What I want to stress in what follows is that it is not *only* due to these practical reasons that the lab has chosen to work primarily with the Ts65Dn mouse. To do justice to their own view of the GCDS mouse as the standard-setting model, Lab X must offer a justification for using the Ts65Dn.

Even though the lab has argued that the Ts65Dn is inferior to the GCDS mouse, the director has spoken fondly of the Ts65Dn after having published the paper on the GCDS model saying that "it's a good mouse, and I think we can show it is a good mouse, but it can't keep up with the fast new mice." Note the task the director sets is that in relation to their own standard for "being a good mouse," the Ts65Dn is not clearly a good mouse. This is because it is not meeting their standards of being a complete genetic model. Their task is to show that the Ts65Dn is just as good as the GCDS mouse (in the relevant ways).

During meetings, the lab has offered two sorts of reasons as to why they work with the Ts65Dn mice in response to my questions. However, these reasons, I would argue, do not suffice to explain why they feel justified in using them, since the Ts65Dn are, by Lab X's own lights, an inferior genetic model. First, there is a set of practical reasons which counteract the difficulties of the GCDS mouse discussed above. Ts65Dn mice are cheap, and the lab does not need to purchase them from other labs in any case because they have a breeding population at their university. The only expenses that the lab incurs from using them are the costs to care for them and maintain the purity of the line. Second, there is a socio-pragmatic reason to use them: the lab

sees this mouse as exemplifying the *current* standards of the DS research community, which is to work with mice that have strong phenotypes and that already have experimental data accumulated around them. Lab X believes that working with these mice gives their claims some extra weight with other labs.

However, turning away from the reasons the lab members have offered to me and to each other, I believe there are additional unspoken reasons why the lab works with the Ts65Dn mouse line, which they hint at times such as when the director said, "I think we can show it is a good mouse." I have cause to think this because working with the Ts65Dn mice does not straightforwardly advance Lab X's agenda to make the GCDS mouse the new gold standard for DS research. I initially wondered whether using the Ts65Dn mouse actually *undermines* the Lab's goal: how could they honestly suggest that the GCDS mouse should be the new gold standard (on genetic grounds) while in practice proceeding on with research as usual with the Ts65Dn mouse (which they regard as an inferior genetic model?). When I asked specifically why they were not using their GCDS mouse in a meeting where they were designing an experiment that would generate data necessary for a grant, the lab director sighed and said, "Well I think we should work with the [GCDS], I think *everyone* should, but we can't. It is just too difficult right now, but the Ts65 is just as good for this." (October, 2015). This, and subsequent observation and interviews, revealed to me that Lab X believes that it is possible to use the comparatively inferior Ts65Dn in a way that still *promotes* the superiority of the new GCDS mouse.

Starting in October 2015, Lab X conducted a series of experiments to show equivalency between aspects of the Ts65Dn and the GCDS. Specifically, members of the lab have focused on showing that APP functions the same way in both models, which stems from the lab's overall commitment to a dysfunction of APP being the primary cause of cognitive degeneration in DS.

However, they have not expressed that this is their goal in print, nor have they said (in print) anything at the level of genetics to justify the Ts65Dn mouse in reference to the GCDS mouse. Nor have they published data on the GCDS mice from these experiments. It was only through being a participant-observer during the planning phases of these experiments that I discovered this particular motivation for conducting these experiments and learned of the GCDS mouse's involvement. Their justification for these experiments rests at the level of showing that the intracellular behavior of APP is sufficiently similar in both models. This establishes that there is an important, though limited, functional equivalency between the two models.

The experiments which established this limited functional equivalency between the two lines have included: showing the presence of Aβ using a vaccine which produced anti-Aβ titers that bound with APP's amyloid plaque-producing substrate; reconfirming their past finding that an overexpression of APP is independently sufficient for neurodegeneration; and deleting the extra copy of the APP gene and measuring its effects on the production of GABA terminal-rich cells in the hippocampus.[78] The combined significance of these experiments was that they established that APP's intracellular behavior in both mouse lines was equivalent. For the lab, this means they can attribute greater epistemic weight to the data on APP they derive from the Ts65Dn mouse. For the purposes of Lab X, Ts65Dn mouse is *as good as* the GCDS.

3.7 The Significance of the GCDS Mouse

[78] Lab X published their data on only the Ts65Dn mice from these experiments; however, in these publications, they did not explain their motivation for conducting them. Their motivation to show equivalency between the GCDS and the Ts65Dn was only expressed through lab conversations and meetings.

To summarize: Lab X has developed a new "genetically correct" Down syndrome mouse model (GCDS) that it rarely uses. Instead, it uses a mouse which it considers to be an inadequate genetic model (TS65Dn) of the condition; however, the Lab has performed a series of experiments in order to show that the inferior Ts65Dn mouse is genetically equivalent with respect to APP in the GCDS mouse, therefore, Lab X has a new justification for the old mouse. Yet, Lab X has not revealed this equivalency explicitly in the papers that came out of these experiments; instead, they only published the data on APP in the Ts65Dn line. The data on the GCDS line has not yet been published. The question which I will explore in this section is two part: First, How does the lab justify working with what they believe to be an inferior mouse model? Following this, my second question is: how does their new mouse line advance their goal of understanding Down syndrome in humans and how does it guide their future work? What I hope to show through both these two subsections is that through the lab's practices, the GCDS mouse has value not just as a concrete model, but as an abstract standard that regulates practice even though it not used in experiments.

3.7.1 Resolving Conflicting Values

The first question is "how does the lab justify working with what they believe to be an inferior mouse model?"

One way the lab has regarded this as justifiable is because it is a practical achievement, not only for then, but for their field that saves members of their field time and resources while offering a way to produce work with greater epistemic weight. As I described earlier, Lab X regards what they are doing as successful and justifiable because they have demonstrated that the

two mouse models are equivalent with respect to how APP functions in three experimental contexts. Since the members of Lab X are concerned with making justifiable inferences to the genetic underpinnings of DS, as opposed to its phenotypic presentation, this demonstration is sufficient to establish limited model equivalency.[79] Furthermore, Lab X is concerned with a subset of the processes in which APP is involved (specifically how Aβ causes plaques, APP's effect on GABA, and its role in neurodegeneration) which further limits what the lab needs to prove in order to establish equivalency between these two mice. Thus, the work Lab X does to show a limited kind of functional equivalency between the GCDS mouse and the TS65Dn mice allows the lab to promote their new mouse as the new gold standard in DS research and use an inferior mouse to meet that new standard. So, even though they are not using the GCDS, they get all the epistemic advantages of working with it while working with the Ts65Dn which is cheaper, easier to breed, and lives longer. Ultimately, they are calling upon their field to either work with GCDS mice directly or put in the work to show that whatever line of mouse they want to use is functionally equivalent to the GCDS mouse.

This call is in-line with a desire in the field to be able to work with a complete genetic model of DS. Due to the genetic nature of DS, it follows that the explanations the field hopes to construct would be grounded in genetics; however, as Lab X has experienced, creating this kind of model is incredibly difficult. These practical problems of developing a model like the GCDS mouse are not unique to Lab X – these are field-wide problems (Gupta et al., 2016). However, the lab's work establishing equivalency between the GCDS and Ts65Dn mouse lines actually

[79] Their goal is to provide an explanation at the level of genetics regarding APP; however, because APP and its substrates are involved with an undefined number of processes in neurons, it is not clear what other proteins (and their substrates) they interact with and if they are also affected by genetic mutations caused by DS. Using the GCDS mouse is a way to weed out which parts and processes in the Ts65Dn line are *not* associated with the genetics of DS as set by the standard of the human genome.

reduces the practical difficulties other labs could face if they were to offer explanations of DS that are grounded in genetics. By constructing a genetically correct mouse model of human DS as a standard, Lab X is giving researchers the opportunity to compare functionally equivalent aspects of the phenotypically strong mouse lines with the genetically correct GCDS mouse (as Lab X did with the Ts65Dn with respect to APP). This would either support a strong inference regarding the causal relationship between genotype and phenotype, or demonstrate that although a phenotype in another mouse line may have had fidelity with an aspect of human DS phenotype, it was *not* produced by a homologous DS mutation.

Either way, if researchers want to continue working with other mouse lines and want their explanations of phenomena to be able to be grounded in genetic accounts, they would need to confirm that the phenotypes they witness have the right cause, i.e. they would have to establish some degree of functional equivalency with the GCDS mouse. Until the functional equivalency is confirmed, the adequacy of the other mouse lines is in question. When I asked the lab director in a meeting if this could put a lot of the "mouse work" other labs have done into jeopardy and not actually prevent the practical problems Lab X had faced, the director clarified that this was an issue of making sure the "tools" of the field were adequate,

> "If you say something is true and you spend a lot of money on it and you don't find what you want, what you said wasn't true. The alternative is that you didn't test correctly. The *tools* are more often wrong than the ideas are… if I said 'I know [Josefina] can fly. I *know* she can fly.' So I say 'Fly [Josefina], fly!' and she flaps her arms and doesn't fly, it doesn't mean I was wrong. Just that the tools were wrong. If I put her on an airplane and say 'fly!' and she flies – I was right. I was *never* wrong, but the method I used was inadequate." (September, 2015)[80]

This was a way of illustrating the likelihood that researchers would discover that, upon comparing their mouse lines with the GCDS mice, the explanations they had provided at the

[80] Josefina is the pseudonym I have given the (at the time) comparatively junior graduate student who the lab director referred to in this meeting. At the time of this meeting, she was the most junior graduate student in the lab.

phenotypic level could not be grounded in genetics homologous to human DS. However, the lab director expressed a belief that this would not be a failure of reasoning on the part of the experimenters and that they could confirm their previous explanations with the GCDS mouse. Furthermore, if other researchers were to use the GCDS mouse, they would be working with a superior tool that would produce results that were epistemically stronger than they were before.

As we have seen, Lab X has two conflicting values. The first is that they value genetic fidelity as the relevant representational aspect in the models they use. The second value is their ability to conduct their work with relative ease. These two values are in tension. What the ethnographic work reveals is how Lab X sought to resolve this tension in an epistemically sophisticated way. Lab X sought to determine whether the Ts65Dn mouse met what Michael Weisberg would call the "representational fidelity criteria" set by the GCDS mouse (Weisberg, 2013, pp. 41). In this case, a criterion of a good model for Lab X is that it must faithfully represent the genetics of human DS. The GCDS mouse is a model and also is a representation *of the standards* a good DS model must meet. Treating the GCDS mouse not only as a tool or a requirement for good DS research, the lab also used the mouse as a standard by which they could evaluate another DS model. Thus, instead of evaluating the phenotype of the Ts65Dn line against the phenomena of human DS, the lab evaluated the Ts65Dn in terms of its similarity with the expression and behavior of APP in the GCDS model.[81] This is noteworthy because, in this case, the previous standard of representing a relevant aspect of the world outside of the lab (the phenotype of DS in humans) is downgraded in favor of the new standard of being equivalent with a relevant aspect of another *model* (how APP functions). The accomplishment of the GCDS

[81] This is akin to Weisberg's use of the term "dynamical fidelity."

mouse goes beyond just the concreteness of the model; instead, the mouse *as a standard* informs and regulates practice without being present in the lab or used in experiments.

By solving this practical problem of not being able to use the mouse line and resolving this tension between their values of good practice, the lab made the GCDS mouse a standard against which one could evaluate other DS mouse models. This is an epistemic success for Lab X and a philosophically relevant feature of modeling practice that was not apparent without participation/observation fieldwork.

3.7.2 The Value of Standard-Setting

The case as I have discussed it so far has only described how the lab has solved one problem. I have not described how this fits into the lab's overall objective of providing an account of cognition in DS in the form of a mechanistic explanation grounded in genetics. This brings us to my second question, "how does constructing a new mouse line as a standard advance their goal of understanding Down syndrome in *humans* and how does it guide their future work?" To answer this question, it will be useful to first put the GCDS mouse in the context of the other possible models the lab has used or has considered. By illuminating how and why the lab values different organismic models to varying degrees, it will reveal how setting the GCDS mouse as a standard actually furthers the lab's work in explaining DS in humans.

Lab X is engaged in a complex determination and negotiation of "ideal" and "non-ideal" norms of success. Continuing to operate at the epistemic level of analysis, I am borrowing the language of ideal and non-ideal normativity from Ben Sheredos, a philosopher of science, who has used this distinction in a discussion on graphical representations of a biological system to

describe to types of normativity one can use to understand scientific practice (Sheredos, 2017, pp. 33). As I apply these ideas here, ideal normativity refers to what is best in a utopic scientific context where practical and ethical constraints do not exist: the only relevant standards are epistemic.[82] Non-ideal normativity refers to some field-wide standard of good practice, but one that is affected by ethical and practical constraints. In other words, non-ideal normativity is the best one can do given the (epistemic) imperfections of reality. Lab X, and their research community, has an implied hierarchy of normative-material biological systems, illustrated in Figure 3.1 and explained below.

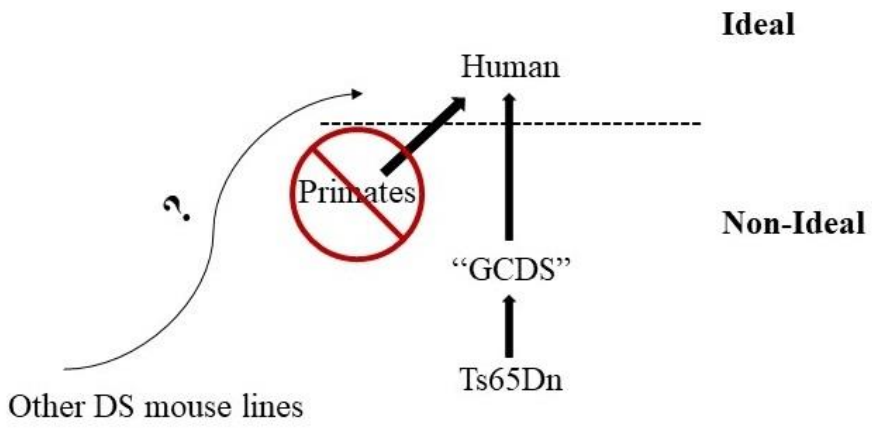

Figure 3.1 "Hierarchy of norms" – This figure illustrates the relationship of normative ideality and non-ideality between the different possible organismic models Lab X could use.

Lab X's work with mouse models in general is not meeting the ideal norm of success for doing work on human diseases. This is because the goal of their research is not to understand how, for instance, the overexpression of APP affects cognition in *mice*. The goal is to understand how this affects cognition in *humans*. Yet, there are several constrains that prevent the lab from working on humans. First there are ethical constraints which prevent researchers from

[82] To be clear, this is my appropriation of Sheredos' distinction and characterization of a "utopic scientific context."

conducting invasive experiments on humans (Burian, 1993; Ankeny and Leonelli, 2011). Second, the human genome is complex and mice are "simpler" organisms on the level of genetics, which makes biological investigation easier (Weisberg, 2012). In an (epistemically) ideal world where Lab X did not have ethical constraints and had a better understanding of the complexities of, and technology to study, human genetics, the lab would be doing work on humans.

In Figure 1, a dotted line separates the ideal (working with humans) from the non-ideal (all non-human organismic models). Since the lab cannot work with humans, the next-best, or best "non-ideal," norm of success for Lab X to meet would be to work with the best non-human primate model of DS due to their close genetic similarity to humans. In such a scenario, the task would be to make an inference (represented by an arrow) from the non-ideal primate model to the ideal of human genetic material. However, Lab X cannot afford to work with primates nor does anyone in the lab have experience working with primates. Also, ethical issues would again arise, precisely because of the similarities between humans and non-human primates. Additionally, it is irksome for many of the lab members to contemplate doing invasive work on primates.[83] Furthermore, there is a field-wide preference to work with, and an accumulation of data around, mice (Burian, 1993, pp. 360). Therefore, the second best non-ideal norm of success is for the lab to work with a complete mouse model of DS, which Lab X would argue is the GCDS mouse. However, as I have described, Lab X also has practical issues which prevent the members from acquiring and working with their new mouse. So, as it turns out, the lab is not

[83] This was made clear to me in a meeting when the director had returned from a conference in which another biologist *not* in the DS research community presented work she had done on mouse lemurs (which are primates). The director suggested it would be interesting to make a DS mouse lemur model. After some uncomfortable silence and searching for images of them online, a project scientist "Pei" exclaimed, "But they're too cute!" (August 14, 2015

able to directly meet their second best non-ideal norm of success. Yet, as the previous subsection explains, they have overcome that hurdle for their purposes regarding APP and have offered a procedure by which other labs could overcome the same practical obstacle. Specifically, they have shown that it is possible to establish a limited kind of functional equivalency between an "inferior" mouse line and the GCDS mouse and, by doing so, the "inferior" mouse line kind be regarded as meeting the new high standard of the new model.

One might think then think that the GCDS mouse was only a transient component of Lab X's practices and this is true. However, the mouse *as a standard* has become an enduring part of the lab's work on DS. The effect of this accomplishment is that it establishes for the lab the precise standards any explanations of DS ought to meet in order to have the strongest epistemic weight. The standard is regulative is several senses. First, it specifies the system in which all mechanisms in DS mouse research must be located even if an explanation was constructed using a limited functionally equivalent mouse model; second, it designates the terms in which explanations of DS must be, i.e. genetic; and third, it offers a resource for evaluating genetic explanations by way of the GCDS line's genome.

Mice, however, are not final organismic model to use before moving onto human genetic material. Before scaling up to work with a more genetically complex animal, the field needs to produce an explanation of cognitive degeneration in DS in a mouse model. Lab X, and other labs, are committed to studying mice so they have a hypothesis to test in organisms that are "closer" to the ideal, but have less data accumulated around them and pose more ethical obstacles. Therefore, by Lab X's own lights, the most adequate explanation, must be developed through research on the best genetic mouse model that the field has. The first step to being able to produce that explanation is to set the standard against which all explanations can be evaluated.

The ideal standard is to use human genetic material and provide an explanation in terms of the human genome; however, this is not a directly applicable standard for mouse research. This is because it is difficult to determine whether an explanation, even a genetic one, using mice got it right. However, by setting the GCDS mouse as an intermediary standard, the field would have a way of knowing whether they "got it right" in a non-ideal sense. Lab X maintains it has produced the best genetic mouse model of human DS, so, as long as it continues to be the best, the strongest explanation the field could produce would be in the context of using the GCDS mouse. This makes the GCDS mouse necessary for future genetic explanations of DS.

3.8 Conclusion

In conclusion, I will return to the methods by which I discovered this case. In the years I observed and participated in Lab X's meetings, both doing informal and formal ethnographic research, I became aware of the GCDS mouse line as well as its value to the lab members and the work they were doing. This did not initially stand out to me amongst the lab's other work that more clearly inquired into the genetic mechanisms giving rise to the phenomenon of cognition in DS. However, the time and resources the lab devoted promoting the GCDS mouse gave me cause to investigate it further through more focused interviews and analysis of their publications. What emerged was a picture of the complex epistemic work Lab X had done to resolve their problem of being unable to use the GCDS mouse. Not only had the lab identified a way to establish a limited functional equivalency between the Ts65Dn and the GCDS mice (and then done so), they also had developed a procedure by which other labs could avoid the same practical problem and get the epistemic benefits of working with the GCDS mouse. Additionally,

the lab had positioned the GCDS line as a field-wide standard for subsequent DS mouse work that simultaneously sets a target and means of evaluation for future explanations, it also constrains future work by designating the system in which they must be demonstrated.

I argue that the philosophical payoffs of better understanding the epistemological function of model organisms is support for using ethnographic methods as a tool of discovery in the philosophy of science. Additionally, using this particular kind of methodology makes accessible the ways in which non-ideal normativity operates in practice. The case I presented here is small in contrast to other ethnographies of science, some of which investigate multiple labs and multiple projects in each (Osbeck, Nersessian, Malone, & Newstetter, 2010). The account I have given barely scratches the surface of this topic. Each lab and each project offers opportunities to gain insight into how norms are created, met, and function in practice. As the movement of practice-oriented philosophy of science solidifies its research program, this is an apt methodology and focus to pursue.

Acknowledgment

Chapter 3, in full, contains a reprint of the material as it appears in "Much Ado About Mice: Standard-Setting in Model Organism Research," *Studies in History and Philosophy of Science Part C: Science in History and Philosophy of Biological and Biomedical Sciences,* 2018. The dissertation author was the sole author of this paper.

Chapter 4

Learning How to Model: Achieving Justification through the Sociality of Experimental Practice

4.1 Introduction

In the previous chapter, I described a case that revealed the standards for mouse models in DS research. That case demonstrated the field's standards because the members of Lab X were explicitly arguing for a change in the standards which the field uses to evaluate mouse models. This forced them to directly address the field-wide standards at play and bring those into contrast with their new standard. In two important ways, this case was not representative of the lab's everyday work. First, it was unusual for the lab members to explicitly challenge those standards. Second, although making animal models is a fairly common practice in the biological sciences, it was novel for Lab X. In the cases I will describe here, the lab members engaged in ordinary material practices that revealed the lab's standards. Unlike in the case of the GCDS mouse, the cases I will describe here involve senior lab members communicating the lab's standards to junior members (undergraduate or graduate students).

In the following sections, I will describe two moments of interaction surrounding regular occurrences in the lab – mouse brain dissection, and isolation and culturing of hippocampal neurons. This chapter serves two interrelated functions. The first is to present two cases from my ethnographic fieldwork that involve the lab members coming together to train a junior member in

a particular material practice that has epistemic significance for the lab.[84] The second function is to show how the physicality and sociality of experimentation allow the lab to make justified epistemic claims.

Regarding the first function, these cases will reveal how the lab members view the learning process in Lab X as requiring an individual to physically and socially work with others, both human and non-human. In these cases, the lab members are discussing experiments using technical language without explaining what certain terms mean. These instances of teaching and education make clearer the standards that the senior members have for biological work. When the junior members made mistakes or revealed they had not yet learned a standard in the lab, the senior members brought the standards to the foreground through their conversations.

As a participant observer in the lab, these moments in which a senior lab member corrected a junior lab member gave me the opportunity to get a clearer window into the lab's criteria for working with models and using them as representations. It also enabled me to see how significant materiality was to the epistemic value of the lab's models. The educational context of these instances brought the standards into view because the lab members had to impart them to the trainees in a way that they would recognize. The standards appeared as recommended courses of concrete action as opposed to abstract policies. Additionally, because, in these moments, the junior members were often not meeting one of the lab standards, the smoothness of the lab's work in which everyone was meeting the standards for good work broke down. The lab members were not able to proceed as usual because a junior member was unaware how things were done. This required the lab's task to shift from doing the work to communicating to a lab member how to approach doing the work. This is not to say that the

[84] I will also supplement and analyze these cases in Chapter 5.

junior members were incompetent technicians. Instead, they either had not learned a specific technique, or the senior lab members expressed that they were not using the correct procedure.

Even though the cases I describe here involve junior members of the lab who are learning from senior members of the lab, they are all fluent in the language of their field. Because I do not want to assume that a reader has a background in biology, I will offer explanations and illustrations to make clear the biological parts and processes they are discussing. By doing so I am attempting to speak from the position of an insider and an outsider (Mol, 2002, p. 1; Alač, 2011, p. 13).

The second function of this chapter is to show how the physicality and sociality of designing and executing an experiment are part of the lab's epistemic accomplishments. I will show how the senior lab members treat material activity as having its own epistemic and communicative significance. A consequence of this is that the protocol for an ordinary experimental procedure is not a mere habit or externally imposed order onto lab life. Instead, it becomes a standard-setting dimension of practice that can be used to assess the merit of a claim as well as a common ground that lab members can use to communicate the significance of their claim. I will first provide an example of such a procedure, specifically the isolation and dissection of mouse hippocampi, and Lab X's instructions for conducting it. In doing so, I will show how the priority of the physical interventions of experimentation is present in even these intentionally generic instructions. In the following cases, I will also show that in the course of the junior members receiving training, they had to present findings or make claims that were grounded in material activity if they were to have epistemic significance.

Although experimentation is a topic of interest to multiple fields, I will situate my discussion in the ethnomethodological literature on following instructions. Much work has been

done on how members of an activity supplement information to "repair" instructions (Markee, 2015) or how laypersons follow scientific instructions (Lynch, Livingston & Garfinkel, 1983; Amerine & Blimes, 1988); however, I will focus on how junior and expert scientists treat the embodied "experiential" and traditionally "cognitive" or "conceptual" components of a set of instructions as significant for the epistemic function of the overall experiment.[85] When I speak of the "experiential," this will be shorthand for referring to the embodied work or material interventions and interactions which occur in the practice of experimentation. When I use the term "conceptual," I am not referring to any philosophical account of concepts, but to instances of purely textual models or information, appeals to categories of objects, or conveyances of a field's theoretical commitments without grounding them in concrete experimentation or findings. While, as I will discuss below, this tracks with Wittgenstein's meaning/use distinction, I also intend to be drawing from Lave and Wenger's discussions on the mutually constitutive relationship between traditional dichotomies such as cerebral and embodied activities (Lave & Wenger, 1991, p. 52). Like Lave and Wenger, I find it useful for the sake of explaining to speak in terms of these kinds of dichotomies to show how ordinary interaction dissolves them.

I will focus on this interrelation between the experiential and conceptual, with additional attention to Lab X's standards for good biological modeling. After each case, I will articulate what standard has come to the foreground and how it was communicated.

4.1.1 Conceptual Distinctions and Chapter Organization

[85] The quotes here are to indicate that this is not how the practitioners would categorize the different kinds of tasks described in the instructions. As I will explain, this is how one might interpret the instructions as an outsider or "stranger" to the lab.

As I will show, a member of the lab learns how to conduct the procedure by doing it under supervision. However, they also receive and have access to a collection of textual resources describing how to do it. In 4.3, I present a compiled and expanded version of the written instructions. An initial distinction I wish to draw upfront, and for which I will later provide justification, is that between "conceptual" and "experiential." As one might expect, these instructions contain the names of numerous biological objects that are part of the discourse of contemporary biology and directions for what to do with them. Attached to these names are meanings and assumptions specific to Lab X's field. For instance, artificial cerebro-spinal fluid, the hippocampus, and a centrifuge are all objects that the instructions do not define and expect the practitioners to be able to identify. The presence of these objects in the procedure convey some of the field's assumptions: 1) Artificial cerebro-spinal fluid replicates the natural fluid around the brain and this is desirable to practitioners; 2) the hippocampus is a distinct region of the brain and is associated with learning and memory (according to Lab X); 3) a centrifuge rapidly spins tubes containing neurons to break up their connections and is sufficient for enabling practitioners to study only neurons. The instructions say what to do with these objects. These kinds of instructions I call "conceptual" because they do not address the experiential realities of working with these objects.

There are other directions that I call "experiential" because they are concerned with *how* a practitioner works with these objects. These sorts of instructions are concerned with the embodied dimensions of what it is like to carry out a procedure. As Unaza, a new undergraduate in the lab, explained to me, these were pieces of information on "how to not mess up." For instance, the authors of the written instructions say how to prevent the hippocampus from sticking to a spoon or whether to worry if their imagined reader observes few neurons in their

new culture. My argument is that these instructions reveal a foundational standard for how Lab X enacts and believes in the adequacy of their models. For the experienced members of the lab, a model is made adequate if it is produced through a specified material practice of experimentation. This, I will show, is because in the context of this lab and its field, a certain kind of material intervention upon a biological object gives it meaning. For the senior members, the distinction had dissolved between the embodied process of executing an experiment and how it is epistemically justified. For them, the experiential and the conceptual are mutually constituting. Additionally, they do not come apart when the biologists evaluate the justification of a given inference. While the lab members perform many physical interventions on material in the lab, I mean to only refer to procedures whose execution happens to enact a field-wide standard. Additionally, the procedure must be a shared or common practice which lab members use as a means of communicating amongst each other the justification of a particular knowledge claim.[86]

By acknowledging how the materiality of experimentation simultaneously has its own intrinsic meaning to the lab members, it is possible to see how a particular material practice serves as a standard and means of communication within the lab as well as to other labs. This is contrary to the idea that meaning exists prior to the experimentation and is applied either before or after that intervention. Instead, I contend that the lab members treat the meaning of their biological research as something that emerges in the course of their everyday bench work. My position is supported by other work which has shown how not all meaning or knowledge is readily, or fully capable of being, expressed through language, such as Michael Polanyi's (1958)

[86] I am not discussing things such as organizing datasets or transporting biological material within the lab or across campus. While these activities require training and planning, these were not explicit matters of concern for the lab members. Because of this, I focused on what the lab members were focusing, i.e. training students to carry out, design, and assess experiments.

work on tacit knowledge[87] and its references to gestalt theory, Ludwik Fleck's (1979) discussions on thought styles and the sociality of knowledge, Chandra Mukerji's (2015) historical account of unformalized "peasant knowledge." My analyses in this chapter add to these approaches by showing how the material activity itself is not a kind of knowledge conveyed to others; but instead is that which makes this community of biologists believe in the representational adequacy of its animal models.

The written instructions for the mouse sacrifice and hippocampal dissection provide guidance for how to physically perform these procedures. They also prescribe how a practitioner ought to value the biological material and think about the epistemic consequences of the physical intervention the biologist is performing. The subsequent cases I present in 4.4 and 4.5 reveal how these standards are born out and enforced in practice. 4.4 will show how these standards are enacted in the context of training an undergraduate how to turn a mouse into a model. 4.6 will provide an account of how these standards are made relevant for lab members training a graduate student to determine the adequacy of her own model.

In the following sections, I will first (4.2) review the bodies of literature on which I will be drawing through this discussion. I will cover what is informing my ethnomethodological approach, ethnomethodological literature on following instructions, and Wittgenstein's conceptions of the mean/use distinction and how this could be applied to the "experiential/conceptual" dichotomy which I have mentioned. Second (4.3), I will present the lab's procedure of dissecting mice, isolating their hippocampi, and culturing their neurons as various written sources describe it. I will do so in order to highlight the juxtaposition of the conceptual and the experiential advice given in these textual accounts. This will be important to

[87] Further applied and articulated by Collins (1974), Mukerji (2006), as well as Joyce (2005) who shows how tacit knowledge is erased in popular narratives.

have in place to show the ways in which this juxtaposition plays out in verbally instructive interactions. It will also be useful to see how the standards for good modeling practice which emerge out of these cases are brought into sharper focus by seeing how the interrelation of the material and the conceptual is grounded in one of the lab's foundational procedures. In "Getting Instructions" (4.4), I will describe how an undergraduate student (Unaza) received instruction on how to sacrifice mice and obtain hippocampal slices. The apparent standard in this was for how to turn a mouse into a model. The standard that I will argue emerges is that one learns to model through doing, not memorizing a list of instructions. In "The Tau Project" (4.5), I describe a meeting in which an advanced graduate student interacts with other lab members in a collaborative effort to settle on her dissertation topic; however, they do not accomplish their goal. The standard that the lab director communicates for evaluating the data one generates with a model is that one must have materially interacted with the model. I will argue this case reveals that "textually compiled" models have a low epistemic status in Lab X, even if they enable a practitioner to offer a mechanistic explanation. To conclude the chapter, I revisit the standards that emerged through the cases and what they can say about how the lab members bring together the conceptual and the experiential in instances where they are evaluating models.

4.2 Ethnomethodology and Wittgenstein

My approach in the following sections is closest to an ethnomethodological one. Ethnomethodology is not a theory or philosophy but is "an empirical research program that investigates recurrent topics that have had long-standing interest in philosophy and social theory" (Lynch, 2002, p. 485). Some of these topics relevant to my work here are: action, meaning, description, and objectivity. Instead of applying a pre-existing framework from philosophy or

critical social theory to understand a case, ethnomethodology studies the everyday methods members in a situation employ in the course of carrying out a range of activities (Lynch, 2002, p. 485). I draw from ethnomethodology because it enables me to focus on how the members of Lab X were engaged in practices of collaborative sense-making (Alač, 2014). Much contemporary ethnomethodological work has turned towards multimodal interaction through using video recording and analysis (e.g. Alač, 2011, 2014, 2016; Bezemer & Mavers, 2011; Licoppe & Morel, 2012; Mondada, 2007). These studies show how talk as well as gesture, gaze, and other bodily conduct unfold in coordination to achieve meaning (Alač, 2014; Goodwin 1994).

The work I present here takes inspiration from these recent studies, especially those which focus on interactions involving scientists or technology (e.g. Alač, 2011; Coopmans et al., 2014; Lynch 1997; Suchman, 2007; Woolgar & Lynch, 1990). However, there is also an earlier tradition within ethnomethodology which used strictly audio recording. My decision to not focus on multimodal interaction stems from the scope of my project. To focus on how lab members communicate and negotiate standards for good modeling practice, I had to look at lengthy discussions, some of which took place over the course of an hour or more. The amount of time it took for a standard to become clear through a conversation precluded analyzing the fine details of talk and gesture. Because of this, my ethnomethodological approach is more similar methodologically to earlier works such as Schegloff and Sacks who made tape recordings of conversations (1973), Garfinkel's recordings of jury deliberations (1949; 1967), or Garfinkel's collaborative work with Lynch and Livingstone on an accidental recording of scientists witnessing a pulsar (1981). I also draw from Garfinkel's explicit use of phenomenological literature which he used in his foundational book *Studies in Ethnomethodology* (1967).

Alfred Schutz was one of Garfinkel's main sources of phenomenological inspiration. In *Studies in Ethnomethodology*, Garfinkel explicitly credits Schutz for influencing his work (1976, p. 36). Specifically, Garfinkel drew from Schutz's discussions on "unnoticed background expectances. [Schutz] called them 'the attitude of daily life.' He referred to their scenic attributions as the 'world known in common and taken for granted'." These background expectancies make certain situations familiar or recognizable as "life as usual" (Garfinkel, 1967, p. 37). For Schutz, these background expectancies allow two people in an interaction to interpret what the other is doing or expressing (Schutz, 1967, p. 110). In his example of someone observing a woodcutter work, he describes how an observer in that situation makes sense out of the woodcutter's action by "inserting [the perceived woodcutting] into his own context of experience" (1967, p. 110). The sense that the observer makes is not given directly through merely witnessing the woodcutting activity. The interpretation is accomplished when the event is synthesized with the total context of his experience and whatever knowledge that experience may shed on the observed event. Garfinkel would call this accomplished interpretation "order*." For Garfinkel, order refers to an "endless" list of topics that pertain to "logic, purpose, reason, rational action, evidence, identity, proof, meaning, method, consciousness…" and is a "practical achievement" (1988, p. 103). Like much of Garfinkel's work, my discussion here is similarly interested in how a certain kind of order, e.g. standards, are practically achieved and maintained in the course of everyday activity.

Another component of Garfinkel's approach, inspired by Schutz, was his notion of how background expectancies "come into view." "For these background expectancies to come into view one must either be a stranger to the 'life as usual' character of everyday scenes, or become estranged from them" (Garfinkel, 1967, p. 37). Garfinkel and his students intentionally estranged

themselves from scenes in everyday life in order to understand the background expectancies that gave everyday occurrences their familiarity. In a series of "experiments," Garfinkel's students intentionally breached the expectations others had for how an interaction would go (1967, pp. 44 – 49). These breaches in expectancies prevented the usual order of things from being achieved and those who were unwittingly part of the experiment sought to reestablish that order. In my time in Lab X I did not intentionally seek to breach the background expectancies of life as usual in the lab and neither did the more junior graduate students. However, in the cases I describe below, the junior lab members were relative strangers to the field in which they were training. Schutz discusses the experience of "the stranger" as one who finds their ordinary way of interpreting and understanding others and their actions as inadequate in the context of a new group (1944, p. 504). Additionally, the new group expresses disapproval at the stranger's way of thinking and asserts that the group's way is "the natural and appropriate way of life" (1944, p. 507). In Lab X, there is an expectation that junior members will not automatically think and act in the way that is normal for the lab. Because of this, the senior members enforce that their ways of doing and evaluating are the appropriate ones. This is how pedagogy works in general – a novice does not automatically come into a new area of study knowing its content or its standards.

Since Garfinkel's *Studies*, some ethnomethodologists have taken interest in how people follow instructions and I position my work in this context. Generally, these studies take place in educational settings. Hellermann and Pekarek Doehler (2010) pick up Garfinkel's interest in Wittegenstein's discussions of uncertain language games (Garfinkel, 1967, p. 70).[88] They focus on instances where new language learners unintentionally redefine a task posed by an instructor due to not recognizing the meaning of some of the instructor's words which defined the game.

[88] For Wittgenstein, a language game, generally speaking, consists of "language and the action into which it is woven (2009, p. 7).

Other work has studied how language learners manage tasks with written or spoken instructions (Coughlan & Duff, 1994). Lynch, Livingston, and Garfinkel more directly addressed instruction in the course of scientific work by studying a man, Schrecker, who had no scientific expertise, but performed lab work by referring to written instruction and receiving spoken instructions from a student with paralysis (1983). This study showed that there was a difference between the reasoning in the text, and the embodied activities Schrecker performed according to the verbal instructions from the student. Hindmarsh et al. similarly describe how the verbal, visual, and tactile are juxtaposed in dental hygiene instruction. In their case, the visual and tactile become ways of "seeing" and "touching" professionally that turn objects into recognizable categories to the field of dentistry (2011).

Returning now to my argument, the more senior members of Lab X interpret the instructions for their procedure such that the conceptual and experiential aspects are essential parts of the same task. Their goal when undertaking this task is to produce a good model. Moreover, Lab X positions the experienced embodied realities of carrying out the experiment as more significant than the conceptual. This is closer to studies which have focused on what instructions presuppose regarding the ability of reader to determine what are acceptable modifications of the text (Amerine & Blimes, 1988). My argument also supplements Lindwall and Ekstrom's work to show how speech and embodied demonstration are seen as "reciprocally intertwined or as standing in a reflexive relation to each other (2012, p. 30).[89] I also extend their account by using Wittgenstein's rejection of meaning/use dichotomy (which I am calling the conceptual/experiential dichotomy).[90] I follow David Bloor's exegesis of *Philosophical*

[89] See also Lynch and Jordan (1995) for additional discussion on how methods, materials, and mechanisms intertwine within the context of molecular biology.
[90] Wittgenstein ends *Philosophical Investigations* with the exclamation that "there is nothing more wrong-headed than calling meaning a mental activity (2009, p. 181).

Investigations in which he says that "meaning is created through acts of use…use determines meaning; meaning does not determine use" (1983, p. 25). I extend Bloor's reading of Wittgenstein to move past "use of language," where language is taken only as speech, and cover other communicative acts such as embodied activity. By doing so, I demonstrate how in the instructions for the procedure of hippocampal slice and culture preparation, the experiential and conceptual components work together to accomplish the task of producing a model. In the production of this concrete model, the lab members effectively dissolve the traditional dichotomies between experiential and conceptual, or the cerebral and physical (Lave & Wenger, 1991, p. 52). I also show how this interrelation of the conceptual and experiential carries through different parts of the lab's work. Additionally, I show how the material activity of experiment has more epistemic significance, in practice, than purely textual claims.

4.2.1 Training in Lab X

While Wittgenstein and the ethnomethodologists take a specific interest in language and talk-in-interaction, I want to also draw attention to an ongoing activity that the lab members are carrying out in the following sections. It is true that they are conversing about how to sacrifice mice, design an experiment, and assess the inferences justifying it. However, all the lab members in these meetings are involved in the activity of training one or more students. The senior lab members are modeling how to value and think about the interrelation between the foundational embodied activities of bench science and the inferences they intend to make and justify through experimentation. The most junior lab members (undergraduates and junior graduate students) are learning how to: 1) be a part of Lab X's social practices, 2) perform particular physical skills, 3) uphold the lab's standards for design and inference-making, and 4) see the interrelation of these

various activities. The advanced graduate students and postdoctoral researchers both help train their junior colleagues as near peers while also being taught how to do this training. While I will discuss training specifically in Chapter 5, because teaching is a clear focus of the interactions I describe below, I want to specifically discuss Lave and Wenger's concept of "legitimate peripheral participation."

Legitimate peripheral participation is a way of speaking about the "situated activity" that is learning. Lave and Wenger want to draw "attention to the point that learners inevitably participate in communities of practitioners" (1991, p. 47). This recognition allows an analyst to discuss the social and material processes by which newcomers enter a community of practice and become increasingly proficient in the skills of that group. Importantly, they emphasize that learning is not the mere internalization of information. While remembering things is certainly an important part of learning, legitimate peripheral participation encourages one to view learning as a set of relations that unfold in an ongoing social world (Lave and Wenger, 1991, p. 50).

Legitimate peripheral participation is relevant for approaching Lab X because its members implicitly reject the traditional dichotomies between learning by doing and learning by abstraction or learning experientially and learning at a distance, as do Lave and Wenger (1991, p. 105). Lave and Wenger's work supports the rather obvious point that memorizing something, such as a list of instructions, is insufficient for knowing how to perform a task. However, more significantly for my project here, legitimate peripheral participation offers a means of talking about the interrelation of activities and kinds of knowing that the lab members bring together as a part of educating a novice scientist. It also offers a way of showing how junior lab members seem to expect that "knowing" something exists on the cerebral side of the conceptual/experiential dichotomy. Part of their integration into Lab X's community of practice

is to participate in the dissolution of this dichotomy through learning how to organize their epistemic work around the lab's standards for models and inference-making.

4.3 The Procedure in Context

In this section, I will provide a description of the written instructions lab members receive for dissecting a mouse and preparing its hippocampus in two ways. This procedure will be the material practice at issue in the cases I present in 4.4 and 4.5. These cases are moments in which senior lab members spoke with junior members regarding the preparation for, or design of, an experiment. In each case, the basic procedure required for the experiment was the sacrifice and dissection of a mouse, plus the culturing of its hippocampal neurons. This is not an exceptional coincidence because almost every experiment in the lab requires hippocampal neurons. Even though this is an important procedure in the lab, it is a routine practice. It is also so mundane that it is often a task given to undergraduates who are working in the lab for course credit or to new graduate students. This not only trains potential future biologists to perform a foundational procedure and exposes them to what real lab work looks like, it allows graduate students and the lab manager ("Lisa") to offload some technical labor. This enables the postdocs and graduate students to have more time to conduct the experiments in which the cultured neurons are used. It also allows Lisa to spend more time managing the lab. This is all to say, the most junior members of the lab have the task of preparing the mice and their neurons. These slices and cultures are then put to work in experiments that more senior lab members conduct. The activity is so routine that even though most of the work the lab does requires the successful execution of this procedure, lab members rarely discuss it directly.

4.3.1 The Procedure as Textually Described

In this section, I will describe the steps of the procedure to dissect a mouse hippocampus and prepare it as slices or as a culture. I am doing this to both explain the procedures which are foundational for the lab carrying out their experimental work and, also, to show how even in the textual descriptions offered in the instructions, the materiality of the procedure is emphasized. I will argue that the directions for embodied activity are interwoven with the conceptual in such a way that the capacity for representation the model has (for the modelers) is in virtue of the material interventions which produced it. The physicality of experimentation gives "meaning" and epistemic significance to the biological material. This is opposed to a theory about the biological material determining how the material will be used or whether it has epistemic significance. I argue that these instructions communicate that a model's adequacy is grounded in the material interventions by which it was produced.

Before presenting the instructions, it is worth first describing Lab X's primary object of analysis, i.e. neurons. Making mouse neurons useable representations of human neurons and neural phenomena is the purpose of the procedure below. Neurons are cells that are specialized to transmit nerve impulses. They transmit these impulses through electrical or chemical signals between each other. The point at which two neurons meet is called the synapse. The structure of a typical chemical synapses are usually composed of an axon and a dendrite. An axon is a nerve fiber and is quite long. Axons extend out from the neuron's cell body and extend to other neurons, muscles, or glands. At the end of an axon is the axon terminal, which release neurotransmitters. These neurotransmitters are produced in the cell body, are packaged into synaptic vesicles, and then are transported through the axon to the terminal where it is then released into the synapse. Whereas axons release chemical stimulation, dendrites receive it.

Dendrites are a branched extension of the neuron. They receive electrochemical stimulation which is transmitted to the body of the cell. Practitioners follow the instructions below to make these neurons useable in their lab work.

The steps, as I present them, are a compilation from multiple sources and with additional detail and explanation for the sake of the reader. This presentation mimics the lab's own practice of presenting a trainee with a patchwork of sources as an initial way of acquainting that junior member with the procedure. These sources were written by practitioners outside of the lab who had significant experience in performing this procedure. The authors' emphasis on the physical realities of performing the procedure mirrors Lab X's own preferences to teach trainees learn by doing. The lab members referred me to several sources they use for teaching students and refreshing their own memory. One of these sources was a paper and accompanying video on the procedure found in the *Journal of Visual Experiments* (Villers & Ris 2013) and the other was an excerpt from a paper in *Nature* (Kaech & Banker, 2006) that a senior scientist ("Alberto") told me was useful because it had a flowchart. A way in which the compilation I present deviates from that of Lab X is my use of bolded words to draw attention to references to the directions for particular kinds of embodied actions and instances where the instructions introduce ethical standards. I do this, first, to show how the conceptual and the experiential come together not as distinct activities, but ones that are interwoven through the practitioner's activity to produce a model. Second, I highlight the explicit ethical norms brought in to show how they are made relevant in the course of the procedure and not something just applied *a priori* or *ex post facto*.

Senior scientists had referred new students to various sources over the years including papers from *Current Protocols in Neuroscience* (e.g. Madison & Edson, 2001) or versions of *Cell Biology: A Laboratory Handbook* (e.g. Celis, et al., 2005). Alberto told me that he liked to

refer students to papers that had short step-by-step instructions found in the more recent literature because he discovered that students grasped lists better than lengthy discussions. Alberto was frequently interested in discussing his mentorship of past students with me, even though he had mentored fairly few in his years at the university. He communicated to me that although there were many sources to which you could refer a student, there was no single source people used to learn the procedure. Instead, a student's eventual understanding of the procedure was a compilation of different presentations of it as well as guided hands-on experience. While I found this statement to ultimately be an accurate representation of the lab's practices, Alberto did not convey the overlapping and interrelated social and material processes that trained a student. He did communicate to me that although the lab manager did compose their own highly truncated version of the procedure, the lab members mainly used it as a checklist after they already had learned how to perform the procedure.

As you will see, the instructions refer to both the standards for conducting the procedure and give precise instructions for the way practitioners ought to grasp, manipulate, and push the biological material in specified manners (e.g. gently, vigorously, quickly) as well as advice for gaining control over the material. I will emphasize these embodied experiential kinds of instructions in bold. As I will show in the subsequent sections presenting my ethnographic data, the material activity of experimentation is more important to the more senior lab members than having information that does not arise out of a lab member's direct experience of working with a mouse model. For example, prior knowledge of exactly where to cut is subordinate to the firsthand experience of holding the mouse and making an incision. Additionally, providing a mechanistic explanation as a result of drawing from other lab's published data is epistemically inferior to a description of biological phenomena based on firsthand experience.

Preparation of Artificial Cerebro-spinal Fluid

The entire procedure is done in a cold solution that preserves the texture and vitality of the brain matter. Practitioners use it throughout dissection and the preparation of the slices. Generally, two liters of the medium is sufficient for completing the procedure.[91]

1. Practitioners are to first weigh the different components, except magnesium sulfate because this is already in the starting solution. JOVE specifies that "**using a standard solution** allows [one] to be sure of the exact concentration of [magnesium] because [magnesium sulfate] in powder is highly hygroscopic. [The calcium magnesium] ratio greatly influences LTP [long term potentiation]".[92] In this context, hygroscopic means that the magnesium sulfate powder absorbs moisture. While it can absorb moisture from the air, which can be problematic when crafting the media, it can also absorb moisture from the dissected tissue, which could cause damage. However, by having a standardized amount of magnesium sulfate already in the solution, practitioners can predictably mitigate this effect. Induction and maintenance and **thus their proportions must always be respected**" (Villers & Ris, 2013, p. 2, emphasis added).
2. Practitioners are to put everything except the calcium chloride in a graduated cylinder and add distilled water until the total amount of the solution is two liters.
3. Practitioners must **stir the medium vigorously** until everything is dissolved. At this point, they ought to add carbogen, which is a gas combination of carbon dioxide and oxygen. They are to wait a few minutes to add the carbogen to the medium and then add

[91] The media is a formulation of 124 mM NaCl, 4.4 mM KCl, 26 mM NaHCO3, 1 mM NaH2PO4, 2.5 mM CaCl2, 1.3 mM MgSO4 and 10 mM D-glucose (Villars & Ris, 2013, pp. 2).
[92] Long-term potentiation (LTP) is the strengthening of synapses in response to patterns of activity.

calcium chloride once the pH of the solution has become stable at 7.4, due to the carbogen.

4. The practitioners are to refrigerate 600 ml in a cold glass dish for the hippocampus dissection. In addition to refrigerating the media in a glass dissecting dish, they must surround it with ice until it reaches 4 °C.
5. The remainder of the media must be filtered and kept in an Erlenmeyer flask which can serve as extra media for the planned procedure or stored for subsequent procedures.

Note in 1 how JOVE refers to a solution which is a pre-given standard. This accomplishes a dual purpose. First, it identifies a solution as both standardized in the sense that it is commonly accessible, basic in formulation, and unnecessary to define further. Second, it identifies it as being a standard in the sense that it does not need to be measured against some other solution to determine whether it is adequate. The instructions carry in them the expectation that a practitioner will see the solution, the distilled water, and the graduated cylinder (in 2) in a way that is specific to their profession with the practices of sense-making that go along with it (Hindmarsh et. al, 2011; Goodwin, 1994). The instructions here are operating at the conceptual level because the objects to which they refer are meaningful solely because of the assumptions the practitioner must bring with them to the experimental space. In 3, the instructions transition from referring to these as objects as having significances imposed by prior knowledge to ones whose meaning can be transformed through the practitioner's work. The practitioner is asked to take these general and standard objects and interact with them in a specified embodied manner by "stir[ring] the medium vigorously." This physical activity combines the solution, the distilled water, and the cylinder into new objects. The solution is no longer "standard" because it is

combined with distilled water, which changes all the objects involved. The cylinder is no longer empty, but full. The physicality of the act transforms these stable objects from ones that were previously not experientially meaningful to the practitioner into a new object which has a unique meaning for the practitioner because of their experience interacting with it.

Preparation of the Dissection Area & Decapitation

1. Next practitioners are to take the dissecting dish filled with cold ACSF out of the refrigerator. They must immerse a previously-refrigerated lid of a glass staining dish, wrapped in filter paper, in the ACSF, making sure to remove air bubbles and oxygenate the media using an aquarium bubbler.
2. JOVE encourages practitioners to arrange the instruments in the order that the practitioners intend to use them. Practitioners should "add three layers of filter paper on the tissue chopper plate." JOVE also suggests that practitioners add "a new razor blade cleaned with distilled water and ether [to the chopper plate]. **The razor blade must be horizontal when it touches the paper**" (Villers & Ris, 2013, p. 2).
3. JOVE outlines an additional step to the preparation of the dissection saying that practitioners ought to "**Attentively check if everything is ready (instruments, temperature ...) because you will not have time afterwards**" (Villers & Ris, 2013, p. 3).
4. Practitioners must **either spray the dissection area** with cold ACSF **or ask someone to do this for them**.
5. Practitioners then must anesthetize the mouse prior to decapitation. They can either use the most commonly used method which is Nembutal IP (100 mg/kg); however, they can

also use halothane anesthesia. The authors of the JOVE article report that they have compared both kinds of anesthesia and determined that they are comparable (Villers & Ris, 2013, p. 3).

In 2, Villers and Ris explain how to prepare the chopper. They seem to assume that a practitioner will know that a chopper can be used to prepare hippocampal slices. They also seem to have the assumption that a practitioner will know how to use it; however, they are offering direction on how to *best* use it. The chopper does not become a new object when the practitioner adds the filter paper or aligns the razor blade, yet these embodied interventions make the chopper serve the purpose dictated by the instructions, which is to produce hippocampal slices. The prior conceptual significance of the chopper combined with the modifications of the filter paper and razor blade are brought together through the practitioner's eventual use of the modified chopper. It is this eventual action which interweaves the experiential and the conceptual to make a hippocampal slice that can serve as a representation to the practitioner. One must assume that the authors of these instructions have written them so that a practitioner can follow the steps to produce an adequate model. Because of this, underlying these instructions is a motivation to produce a model (Schutz, 1967, p. 28). The direction of how to prepare the chopper is motivated by the goal of producing a good model. When a member of Lab X follows these instructions, they step into and take on this motivation complete with the standard for achieving the end goal.

In 3, JOVE encourages practitioners to check that everything is ready because they will not have time afterwards during the rest of the procedure. This is noteworthy because Villers & Ris are not providing directions for specific physical interventions upon the brain. Instead, they are offering instruction regarding to what the practitioner should pay attention. This is similar to Hindmarsh et al. (2011) and Goodwin's (1994) descriptions of how people are taught to see, or

learn to see, as a member of a given profession. The instructions that JOVE offers do not require any specific tangible change to the experimental space; instead, it gives directions on how to look at the space and what to take into consideration. As a proficient instructor would, the instructions also give a reason for why the practitioner ought to make sure everything is in its place (Lindwall & Ekstrom, 2012). In this case, the reason for surveying the dissection area at this point in the procedure is because the practitioner will not have time to do this later during the sacrifice of the mouse, the removal of the brain, and its preparation. This implies that the practitioner will have to have their attention on the tasks at hand and that there will be little break in between them. The instructions do the work of anticipating a future experience of the practitioner while also cautioning the practitioner against distracting retrospection in the next steps (Livingston, 2017, p. 106). These directions work toward mitigating the possibilities of how a practitioner could fail to execute the actions the instructions command and thereby fail to produce an adequate model.

Brain Removal

1. Practitioners are to use a guillotine to decapitate the unconscious mouse. Villers and Ris state that the "decapitation must be performed under anesthesia but cervical dislocation can also be used. However **cervical dislocation needs a very good practice to avoid animal suffering** [sic]" (2013, p. 3). This cervical dislocation is different than using only a guillotine. Cervical dislocation refers to a practitioner applying pressure below the skull to quickly separate the spinal column from the skull and brain. This provides a faster and painless death for the animal if done correctly.
2. Practitioners then must "**dissect the mouse as quickly as possible**" while spraying ACSF continuously either manually or using an automatic shower (Villers and Ris, 2013, p. 3).

3. After completing the previous steps of preparing the ACSF, the dissection area, anesthetizing the mouse, and decapitating the mouse, practitioners may then dissect the mouse. To do this, the practitioners are to first "**while holding still the head with the index finger and the thumb of one hand on the muzzle**," they then are to use dissecting scissors to make an incision along the middle of the top of the mouse's head through the skin and fur (Villers and Ris, 2013, p. 3). This cut should start at the edge of where the guillotine decapitated the mouse.
4. Once this initial incision has been made, the practitioners then must "**cut through the cutaneous muscle on each side of the head** to fully expose the skull plates and remove the muscles at the caudal [or backside] side of the head" (Villers & Ris, 2013, p. 3). This incision is horizontal, meaning that it is around the side of the mouse's head, whereas the previous incision was sagittal, i.e. vertical.
5. Using the dissecting scissors, practitioners are to then cut the temporalis muscle on each side of the mouse's head. Then, "along the temporalis plate… cut the frontal plates in the middle, transversally. Then, **make a little cut** on the occipital bone, between the two plates" (Villers & Ris, 2013, p. 3). During this phase of the dissection, the practitioners will first cut through the muscle and then through the bones of the mouse's head.
6. Practitioners then must cut the backside base of the occipital plates. This is at the back of the mouse's head.
7. Practitioners are to use spring scissors to cut the connective tissue between the two top plates of the mouse's skull.
8. After cutting this tissue, the practitioners are to then use forceps to remove the skull halves by "**spreading them away from each other**" (Villers and Ris, 2013, p. 3).

9. Practitioners are to use a scalpel to make a cut after the olfactory bulb of the brain and just before the cerebellum. This separates the cortex from the olfactory bulb which is towards the front of the mouse and the cerebellum and spinal cord which is at the back of the head. Practitioners are to then release the cerebral cortex from the rest of the mouse. Practitioners are then able place the extracted brain into the dissecting dish with cold ACSF.

1 offers ethical reasons for performing certain actions. In 1, the instructions offer two ways of decapitating the mouse. The simplest is by using a guillotine; however, it is also possible to perform a cervical dissection. The instructions specify that a practitioner has to use "very good practice [sic]" because there is a higher chance for animal suffering with this procedure if performed incorrectly. The instructions do not say that the suffering of the mouse could affect the quality of the neurons derived from the procedure. It appears that Villers and Ris are considering the ethical dimensions of animal sacrifice and are introducing them explicitly to create a decision point for the practitioners regarding what they will physically do next. In 3 and 8, the instructions give specific guidance regarding how to hold the mouse and what the practitioner needs to do with their hands and tools. These directions are made specific to the practitioner by contextualizing the required actions to their body. If the instructions were more abstract and told the practitioner to just cut the top of the mouse's head, it would be unclear whether to cut the crown area of the mouse or around the nose. What counts as the top would depend on whatever orientation the practitioner had to the mouse (Livingston, 2017, p. 102). Instead, the instructions use the hand of the practitioner as a way of articulating the correct orientation of the mouse's head. These sorts of practical directions make possible the actions for which the instructions call and, furthermore, provide a way for a practitioner to confirm whether

they are correctly dissecting the mouse and, therefore, producing an adequate model. For instance, they are able to verify that they are cutting the middle of the mouse's head by checking to make sure their body is positioned the way in which the instructions dictate.

In 8 the instructions shift from using the practitioner's body as a way of determining the correct orientation of the mouse to using the organization of the mouse and its brain as a way of guiding action. In this step, the instructions also begin to use more specific language to describe exactly how a practitioner ought to be manipulating the mouse. In this case, the practitioner ought to "push" the skull halves apart as opposed to language that does not so clearly imply embodiment, e.g. "remove the skull halves" or "use the forceps to remove the skull halves."

Hippocampal Dissection

1. After practitioners have placed the brain in the ACSF-filled dissection dish, they then use the scalpel to sever the two hemispheres by inserting it between the two lobes.
2. Practitioners must use a binocular surgical microscope to view their dissection of the hippocampus. The instruments they use to isolate the hippocampus are two small spatulas. Practitioners first select one hemisphere and **"carefully spread"** its structures to reveal the lateral ventricle (Villers and Ris, 2013, p. 3).[93] The lateral ventricle is a large C-shaped cavity in the brain that is filled with the mouse's cerebral spinal fluid. The hippocampus is located underneath the floor of the bottom curve of lateral ventricle, so by finding this cavity the practitioner is able to locate the hippocampus without risking damage to it. After locating the later ventricle, the practitioner removes the brain stem and diencephalon (which is located above the hippocampus and is composed of the

[93] They are not "digging" through the top of the brain here because this would imply that they are gouging portions out of the brain. The practitioner, instead, makes their best effort to use the small spatulas to push aside segments of the brain along its natural divisions to find the open space of the lateral ventricle. The tissue can be stretched here; however, the practitioner tries not to tear anything.

hypothalamus, thalamus, and epithalamus). "**This is done by applying the spatulae on the frontal cortex** [front of the brain] **on one side and on the diencephalon** [back of the brain] **on the other side.** [Practitioners also ought to] **take care to not touch the hippocampus with the spatulae and to not stretch it during tissue sectioning"** (Villers and Ris, 2013, p. 3).

3. Practitioners then are to sever the connective tissue between where the hypothalamus was and the hippocampus. This enables practitioners to free the hippocampus and be able to **gently push the hippocampus** out of the cortex. It should be able to **"roll away"** when practitioners insert a spatula inside the lateral ventral and pushes against the bottom floor of it (Lab X internal instruction document).
4. Once the hippocampus has been extracted, practitioners are to remove extra tissue and blood vessels.

At this point, practitioners encounter a choice-point of whether to prepare the hippocampus as slices or as a culture. This is something that a practitioner, or their supervisor, would have chosen prior to them entering the lab. If the intended experiment is one that involves studying synapses or the natural organization of brain tissue, practitioners will prepare hippocampal slices. If the planned experiment is intended to study how tissue organization develops, requires only a single kind of cell, e.g. neurons as opposed to glial cells, or would be simplified by working with only one kind of cell, it would be best to prepare a culture.

Cutting of the Hippocampal Slices

1. To begin cutting the slices, practitioners are to first use a wide-mouth pipette to transfer the hippocampus into a spoon.

2. Practitioners are to then use a standard pipette to suction away the extra fluid surrounding the hippocampus.
3. Practitioners then are to deposit the hippocampus on to the chopper (the device used to slice the hippocampus) by tipping the spoon vertically down so that it nearly touches the filter paper. The practitioner then proceeds by "**rapidly touching"** the hippocampus ("**at the tip of the spoon"**) on to the paper. This allows for the hippocampus to "**barely stick to the filter paper and gently deposit"** the tissue (Mathis et al., 2011, p. 3).
4. Practitioners have the choice of using the chopper to slice the hippocampus; however, they are also permitted to use a vibrating microtome or a gravity-controlled chopper (Mathis et al., 2011, p. 3).
5. If using a chopper, which Lab X uses, practitioners must lift the filter paper with the sliced hippocampus and "**spread the slices a little**." Then, they are to spray the slices with ACSF "**to free them**" and transfer them to an ACSF filled petri dish (Villers and Ris, 2013, p. 3). If a vibrating microtome has been chosen, the recommended method of transferring the slices to the petri dish is **with a brush**. Mathis et al. caution that "**one problem with this approach [using a chopper] is that the hippocampi can move between chops resulting in uneven sections. Also, be careful to remove as much white matter, and especially as much vasculature, as possible before chopping. This material will stick to the brush, the razor blade, or both, making slice transfer very difficult and increasing the probability of stretching or damaging the tissue**" (Mathis et al., 2011, p. 3*)*. Practitioners are to be careful to remove as much white matter[94] from

[94] White matter is the pale surrounding tissue of the brain consists mostly of nerve fibers. The gray matter is the target of interest. In the case of the hippocampus, there is white matter on its anatomical top that needs to be removed. The white matter contains the cell body of glial cells as well as the axons from neurons. The gray matter is primarily composed of neuronal cell bodies, which the target of interest for Lab X.

the hippocampus as possible because it has the "**tendency to stick**" to the practitioner's tools (Mathis et al., p. 3).

Culturing Neurons

1. Instead of preparing hippocampal slices, practitioners have the choice to prepare a culture of hippocampal neurons. They are to first place the intact hemispheres into a drop of CMF-HBSS (which is a balanced salt solution). They then are to finely chop the tissue with scissors. Practitioners should cut the tissue "**as finely as possible**" (Keach and Banker, 2006, p. 2410).
2. They are to transfer the chopped tissue into a 50ml centrifuge tube, adding in an additional 12 ml of CMF-HBSS as well as 1.5 ml each of 2.5% trypsin (which breaks down proteins) and 1% DNase (an enzyme which degrades DNA). Practitioners are to then incubate the tube in a 37° C water bath for five minutes while occasionally swirling the tube.
3. Practitioners are to then further refine the tissue by "**sucking up the solution"** and squeezing it out 10–15 times in a 10-ml pipette (Mathis, 2011, p. 3). Next, they return the solution and the tube into the water bath for another 10 minutes, continuing to "**swirl occasionally**" (Keach and Banker, 2006, p. 2410). They are to repeat this process again until most chunks have disappeared. This process not only refines the tissue into similarly sized pieces, it also breaks the connection between individual neurons.
4. Next, practitioners are to pass the fluid through a cell strainer to remove chunks of tissue that cannot be further refined. They are to collect what passes through the strainer in a 50-ml conical tube containing 15 ml glial medium.

5. Practitioners are to then spin the tube in a centrifuge for 5–10 min at 120G to remove enzymes and lysed cells. A lysed cell is one that has had its membrane broken down. By removing both of these, practitioners are left only with the medium in the tube and intact cells. The practitioner then discards the liquid above the tissue in the tube because it is the liquid which contains enzymes and lysed cells. Practitioners are to add new artificial cerebrospinal fluid the tube.
6. Practitioners must then determine the cell density of the new solution.
7. Practitioners are then to plate the cells, adding 15-20 ml of artificial cerebrospinal fluid per dish.
8. After one day, practitioners must **"feed"** cultures with fresh artificial cerebro-spinal fluid. First, they must "**swirl the flask or dish to remove loosely attached cells**". They then are to remove the medium and replace with fresh medium. Kaech and Banker reassure practitioners by saying, "**when inspecting cultures at this stage, do not be alarmed** by the sparseness of the culture and the amount of cell debris. The astrocytes you want to expand remain firmly attached to the flask surface and will proliferate quickly" (Kaech and Banker, 2006, p. 2411).[95] It is important that there are astrocytes in the cell cultures because they maintain the health of the neurons in the culture.
9. Practitioners must continue to "feed," i.e. add new medium to, the culture every two to three days, making sure to **"slap the flask 5–10 times against your hand to dislodge loosely attached cells"** before adding fresh medium (Kaech and Banker, 2006, p. 2411).

[95] Astrocytes are different than neurons. There are several different kinds of cells in the brain, one of which are astrocytes. They are thought to be responsible for providing nutrients for other cells, maintaining the ion balance in the brain, and are involved in the overall health and maintenance for surrounding cells.

These are “textbook” descriptions of the procedures upon which Lab X relies to conduct their experimental work. I have described this overall procedure, first and foremost, to familiarize the reader with the technical language of the lab and to explain the procedure that is essential for the lab’s more advanced experimental work that they use to make claims about Down syndrome or Alzheimer’s disease. Even though most of the cases I describe below do not reference these instructions, it is these instructions as they are enacted that are necessary for the experiments they do talk about. In other words, in the experimental work they discuss, this procedure has already been accomplished or needs to be.

Second, I wanted to show how these textual instructions for making a neural model communicate a standard which dictates both how to produce an adequate model and the epistemic significance accorded by hands-on experimentation.

Third, I wanted the reader to see even in the instructions for a basic procedure there is a juxtaposition of the conceptual and the experiential. Additionally, neither the experiential nor the conceptual are set aside as different tasks or are regarded as being subordinate to the other; instead they are interwoven. By establishing their juxtaposition, it will be possible to show how this relationship occurs not only in the text of the instructions, but in the conversation between the lab members. Through these conversations, it becomes possible to see how the senior lab members value the practical material activity of experimentation not as a way of creating a product to which they attach meaning after the fact, but as a meaning-making process. By attending to these conversations, it also becomes possible to see the lab’s standards for what is important in modeling practice and what is sufficient for an epistemically strong model.

4.4 Getting Instructions

This section describes how a new undergraduate student in Lab X received instruction on how to perform the procedure in the previous section. Through this case, I will show how the lab communicates its standard for how a lab member ought to turn a mouse into a model. In short, the standard for turning a mouse into a model is following the instructions for this procedure. I will argue that this case also reveals a standard for learning how to make a model in this lab. I focus on how "Lawrence," the lab director, redirects the undergraduate from her preoccupation with memorizing the written instructions to focusing on the physical doing of the procedure. The standard for having learned the procedure that emerges from this exchange, I contend, is not by merely to have studied the instructions. Instead, the lab's standard for learning is to be brought into the everyday social and epistemic practices of Lab X, both of which have traditionally experiential and conceptual components.

In September 2015, a new undergraduate student, "Unaza," started working in the lab for course credit. Unaza was a junior at the university and a pre-med student. She had worked in the lab before with one of the senior scientists ("Bai") as part of the lab requirement for one of her biology courses. According to the senior scientists, she had shown aptitude for lab work and had inquired about graduate programs in biology. The senior scientist had spoken to Lawrence who invited her to work in the lab to receive course credit and a small stipend. Both told me that she was there so she could see what it would be like if she were to combine her interest in pursuing medicine with her interest in bench science. Unaza only attended meetings and worked in the lab sporadically throughout the academic year, due to the university having issues processing her student visa paperwork. However, by Spring of 2016, she was able to regularly attend meetings. In a meeting on May 18th, the lab director asked her to prepare hippocampal slices of a Ts65Dn

mouse and observe a graduate student culture its neurons. This would contribute to one of the experiments the lab conducted in order to establish a limited functional equivalency between the Ts65Dn and GCDS mouse lines.[96]

As was our habit, Unaza and I sat next to each other in the lab meetings when she attended. It was because I was sitting next to her that day that I noticed that she became very tense when Lawrence said,

"Unaza, I think it's about time we had you prepare some hippocampal slices."

"So, I have to… sacrifice the mouse too?"

"Yes, and collect a urine sample beforehand."

The lab manager, Lisa, joined the conversation assuring Unaza, "It's okay. It really isn't difficult to get a urine sample from them. Basically, you just turn them over and use a pipette. Some of them don't really like to be held but getting urine doesn't actually bother them." It was unclear to me whether Lisa had noticed Unaza expression of discomfort at the prospect of sacrificing a mouse or if she had assumed that Unaza would be concerned about the additional task she was being given.

"Oh, okay," Unaza replied, while fiddling with her hands.

"Lisa will give you some instructions," Lawrence said.

The next lab meeting was two days later and Unaza came to that meeting with a sheet of paper that had creases from having been folded into eighths. I had the impression she had been carrying it in her pocket. It appeared to be a list and she had made annotations in the margin and

[96] Specifically, the work Unaza performed would contribute to the experiment which used a vaccine in order to show the presence of Aβ in neurons that were from Ts65Dn and GCD mice. The point of this experiment was to show how much Aβ was present in a neuron. The lab compared the results from the Ts65Dn mice to that of the GCDS mice. They were also able to show the utility of the vaccine for labeling Aβ in *in vitro* neural models.

underlined certain items on the list. The items on the list were short and filled with technical language that I hadn't encountered before. I asked,

"What's that?"

"These are the instructions for preparing the hippocampal slices that Lisa gave me."

Apparently, Lisa giving instructions to Unaza had amounted to Lisa handing Unaza a sheet of abbreviated instructions. Looking over her shoulder, it contained significantly abbreviated versions of "Brain Removal" and "Hippocampal Dissection" in 4.3. After the Friday meeting, I researched what went into the procedure and looked through one of the lab's handbooks on how to sacrifice a mouse. I had also asked another graduate student in the lab, Josefina, what the standards for the procedure were and she said she mostly learned by watching a video on JOVE and asking Shirley, the "mouse person," to help her at first.

"Oh! How are you feeling about the whole thing?" I asked.

"Well, I'm nervous, but I've studied them a lot, but I'm not sure about some things." In the course of the meeting, Lawrence asked Unaza if Lisa had told her how to perform the procedure. Unaza said yes and held up her set of instructions while expressing her concern about damaging the brain. She expressed particular concern about where exactly she should cut the mouse. Lawrence listened and said gently,

"Don't worry." He waved his hand at her instruction sheet as if he was brushing it away, "I'll show you how to do it."

The next week I asked Unaza how it had gone, and she said that the director had walked her through it. She said it had been fine and that the director had been "really nice about the whole thing." She seemed quite relaxed. I did not push her to talk about the sacrifice and dissection in particular. I did ask about whether she learned exactly where to cut and she paused

before saying casually, “Oh, yeah. I did.” From speaking with her, what stood out more to her was how easy the procedure had ended up being and how Lawrence had explained how her actions corresponded with producing things they could measure later. Overall, her concern about where to cut became less significant within the context she now saw her work. She was no longer concerned about figuring out exactly where the instructions said she should cut, but how she could best prepare hippocampal slices in a way that facilitate other lab members’ work. She mentioned that she learned how to label dishes that contained the slices and how to store them. Before turning our attention to that day’s meeting she said, “It is just so important to make sure the slices are clean because sometimes it takes a couple of days for someone to get to it. If you don’t do it right, it might be useless later or even contaminated and then nothing they do is right.”

The initial standard that is apparent from this case is that for someone to make a model, or something which has the capacity to serve as a model, one must complete the procedure I described in 4.3. This was demonstrated through Lawrence first saying that it was time for Unaza to “prepare some hippocampal slices,” which was followed by Lisa providing a kind of instruction. This initial instruction happened to take the form of a sheet of paper which had an abbreviated form of the procedure I outlined. Unaza did not seem to view these instructions as one possible way of preparing the hippocampal slices, but as *the* way to do so. This was indicated through Unaza’s explanation to me that the sheet of paper contained the instructions that Lisa gave her. Her annotations and the well-worn quality of the paper led me to believe that Unaza saw these as what she had to do in order to prepare the hippocampal slices in a way that would be useable by the other members of the lab. Her stress and diligence made me think that she thought that she would be expected to know how to do the procedure after having read the

sheet. Without questioning it, she seemed to assume that she was expected to merely internalize the directions.

I argue that Unaza's concern about her own ability to perform the procedure created an interaction in that meeting which more fully brought to the foreground the lab's standard for learning. Lave and Wenger's work would support the interpretation that Unaza's misconception about what was expected of her gave the lab members an opportunity to implicitly emphasize their desire for her to engage in legitimate peripheral participation. Furthermore, this meeting gave Unaza, and me, insight into this community of practice's expectations for learning. When Lawrence casually waved of his hand to dismiss the sheet of instructions saying, "Don't worry. I'll show you how to do it," he redirected the priority Unaza was giving to the textual instructions. No one expected her to have come into that meeting having the ability to perform the procedure. Instead, Lawrence took her misconception of the lab's standards for learning as an opportunity to signal the importance of him walking her through the procedure.

If he had expected her to be able to perform the procedure based on her attempts to internalize the textual instructions, he could have explained exactly where to cut the mouse, which perhaps a more complete set of textual instructions would have provided. But he prioritized the material act of conducting the procedure as the way to answer her question. Performing the procedure with Lawrence's guidance did seem to resolve whatever apprehension Unaza had. After having conducted the procedure, Unaza did not have questions about how to prepare the hippocampal slices nor did she express concern about exactly how to do it. Instead, she came away from that time with Lawrence with concerns that revealed her understanding of the sociality and commonality of the work the lab members did. While it certainly is important to cut in the mouse in the right place, it was more important to Unaza that she label the dishes and

make sure they weren't contaminated. While following full instructions for the procedure ensures these results, Unaza seeing how her performance fit into the lab's community of knowledge production gives special significance to certain parts.[97]

Turning to Bloor's interpretation of Wittgenstein, the textual instructions could be seen as not having a clear meaning because they did not have any relationship to an activity Unaza had undertaken (1985, p. 25). While the words on the page were intelligible to Unaza, they did not have a referent *for her*. In Wittgenstein's account of the "builder's language" the words such as "slab" or "beam" do not intrinsically *mean* or refer to certain objects. Instead, "slab" refers to a slab because this meaning was achieved when the builders agreed that "slab" would refer to a certain object. Furthermore, these objects could be distinguished by how the builders used them, not initially by what words were used to refer to them (Wittgenstein, 1953, p. 6). For Unaza, she knew the words on the sheet, but she had not yet done work with mice that would make them meaningful in a way that would enable her to answer her question of where to cut the mouse. The sheet she received did not have the detailed directions of my presentation of "Brain Removal," which specifies how a practitioner ought to hold the mouse's head to know where to cut. Lisa's abbreviated instructions would, perhaps, have been clearer to someone who had prior experience conducting the procedure (Amerine & Blimes, 1988). But without even a description of how to physically proceed to perform the action, a novice would not be able to use the instructions as a means of knowing where to cut. Lawrence answered this question by giving Unaza the experience of performing the procedure which would enable her to give meaning to

[97] This includes the instructions' instance that the razor blade must be cleaned with distilled water or a new razor blade be used each time. Both of these minimize the reduce of contamination. Additionally, insisting that someone continuously spray cold ACSF also reduced the risk of contamination. Because contamination is such a serious issue, it is actually a very useful suggestion to have it implied that if one isn't capable of doing the dissection and spraying the ACSF at the same time, one should ask someone to help.

the language of the instructions (Goodwin, 1994; Hindmarsh et al., 2011). In this way, Lawrence pushed Unaza to engage in legitimate peripheral participation as opposed to her first inclination, which was to merely memorize the instructions (Lave & Wenger, 1991). This had the dual effect of involving her more fully in the lab as a community of practice as well as exposing her to the profession's standards for how a biologist ought to approach basic lab work.

Thus, for one to know how to perform this procedure, one must have done it in such a way that one is able to make meaningful the language used to categorize the experience of doing the procedure. Most importantly, the standard for having learned the procedure is to have performed it in such a way that one can recognize the way this activity functions within the community of knowledge production in which it occurs.

4.5 The Tau Project

This section describes how a graduate student in Lab X attempted to justify an experiment she wanted to conduct by offering a mechanistic explanation. In this case, the other lab members determined that even though she had offered a mechanistic explanation, it was not sufficient for justifying the expense of conducting the experiment. Ultimately, they deemed that the mechanistic explanation was itself unjustifiable because it relied on data compiled from three different published papers instead of producing her own data. Moreover, these papers used different kinds of animal models. Through presenting this case, I will show how the lab communicates its standard for giving data sufficient epistemic merit to justify a commitment of lab time and money. This standard is that a lab member needs to have physically conducted the experiment or be able to discursively construct what must have happened to carry out the experiment. Furthermore, the other lab members need to agree that the physical procedures were

acceptable or that the discursive construction, or reconstruction, is plausible. In this case, the graduate student would have need to conduct the procedure described in 4.3. I will show how the lab values mere descriptions of phenomena, if a lab member conducted the experimental work themselves, over a mechanistic explanation compiled from externally published data. I contend that this valuation stems from the field's practice of taking into account the material history of a model. This case builds upon the articulation of how the standards in 4.3 and 4.4 play out during a model's assessment and shows that, what I call, "textually complied" models are inferior to material ones.

I also contend that this case supports my interpretation of the instructions in 4.3 which I see as communicating standards for how to bring together dimensions of practice which are traditionally embodied with the conceptual to produce an adequate model. Additionally, I will argue that this case reveals a standard by which lab members are expected to evaluate their own model's adequacy. For a model to be adequate in Lab X, the lab members must be able to either physically produce a model or be able to discursively construct what must physically and epistemically happen to produce a model. The graduate student in this case is in the position of trainee and is learning how to evaluate her own model. What emerges in this section is that she came into the meeting with well-developed conceptual standards for assessment; however they were not connected to the materiality of the models or the epistemic culture of Lab X. Through the disagreements the graduate student has with the senior lab members, the lab members bring to the foreground and clarify their standards. For them, the adequacy of a model emerges through the discursive construction or reconstruction of the material practices involved in experimentation. The embodied work of producing a model mutually constitutes the conceptual dimensions of the practice that are both grounded in a field that finds common ground in the

significance of these shared activities. This shared practice of meaning-making serves as a standard by which one can evaluate a model and the inferences one wants to make with it.

At the beginning of 2016, Lawrence proposed that some lab meetings be devoted to reading current literature chosen by graduate students that related to their research. These meetings, he said, would be a small journal club, but the point of them would be for the papers to influence the graduate students' projects. It would also have several additional benefits, such as giving the graduate students an opportunity to practice reading and presenting articles. This would also keep the more senior members of the lab apprised of the latest work in the field, without having to spend a great deal of time searching for it or reading it. Additionally, it would allow other members of the lab to know what the various students in the lab were doing and keep track of their progress. Also, Lawrence said, this would be particularly useful for the graduate students who were still settling on "their project."

Even though graduate students entered and graduated during the time I was in the lab, there was rarely any mention of them working on a "dissertation." Instead, they described what they were doing as working on their "project." The senior lab members' goal was for graduate students to start their project before they advanced to candidacy and continue working on it as their dissertation research. Part of their advancement process was to present their project proposal to their doctoral committee. In the neuroscience program, graduate students met with their full committees several times before they defended their project proposal in their "exam," which, if they passed, would allow them to advance to doctoral candidacy. While there was certainly some dread around their advancement examination, the main concern students expressed was about packaging what they had been working on during their time as graduate students into a coherent project. Often, the proposed project a graduate student defended during

their exam was not the project they ended up completing for their dissertation. This could happen for several reasons, which Josefina articulated to me prior to her own advancement to candidacy.

Sometimes a student would need to advance to candidacy to be eligible for funding from a particular source and the proposed project served as a demonstration that they could formulate and defend a project. Other times someone in the field published on the topic after the graduate student defended, making it redundant for the student to pursue that as their dissertation project. Finally, and most frequently, the graduate student's interests would shift, or they would begin the project and discover that they were not able to get the robust results they thought they would get. Because of these factors, graduate students often took over a year after advancing to candidacy to have a clearly defined project. [98]

One student who did not have a clearly defined project for some time after her candidacy defense was a seventh-year student named "Shui." Unlike the rest of the graduate students in Lab X, who were in the neuroscience program, Shui was technically in the biology department and had worked in another lab for several years. Shui had been interested in neurobiology throughout her entire graduate studies; however, the previous lab she had been in primarily conducted behavioral tests as a way to study olfaction. Although she had advanced to candidacy in her third year, it was not until her seventh year (her second in Lab X) that her project took a clear shape. This is not to say that she did not contribute to Lab X. She often put long hours into lab work and assisted senior scientists and project scientists on their research. She had spent several months

[98] My first-hand example of this is Josefina, who was a fourth year when I first started attending lab meetings. Although she was clear that she wanted to work on axons, she was not clear on what about them she wanted to study. During that year she studied the growth of axons in neurons in DS vs. non-DS *in vitro* models. However, after she advanced to candidacy, her work became more focused on axonal trafficking and signaling in DS models. Regarding the other graduate students, I was only present after they had advanced to candidacy. The generality of the claim I offered here was is based on conversations I had with senior scientists and Josefina.

attempting to clarify her project. Out of all the lab members, she presented articles the most often in the journal club meetings the lab held.

Here, I will focus on one that took place at the end of August. In the following chapter, I will discuss the one that took place at the beginning of October. I have selected this first meeting, described here, because Shui presented the articles as ways to justify the project she was proposing she do as her dissertation research. In the first journal club meeting, the more senior lab members reasserted the standard communicated in 4.3, i.e., for a model to be adequate, a lab member must physically create it. Alternatively, they must be able to discursively construct the material activities that produced the model, or discursively reconstruct it if they are relying on published results, in a way the rest of the lab agrees is plausible. This builds on the further articulation of this standard revealed in 4.4, which implies that knowledge or meaning making comes out of embodied action. In this case, the standard that emerges is for evaluating one's own model.

In the August meeting, Shui was responsible for being on deck and chose three papers to present. This was an ambitious number of articles because these meetings often became a Socratic dialogue between the graduate student, Lawrence, whichever senior scientists were attending the meeting that day, and the more advanced graduate students, such as Josefina. These were instances where senior members were training newcomers in their community of practice. The more advanced graduate students and postdocs were near peers, both training the newcomers and receiving training on how to mentor others in their field (Lave & Wenger, 1991). Through the kinds of questions the director and other members would ask, it was clear that there was an expectation that the students knew the material they were presenting backward and forward and that they would not spend time in the meeting hunting for information in the paper. Because I

had observed previous meetings where the lab members did not go easy on graduate students who were presenting more than one paper, I was surprised that Shui had selected so many papers. As I have said, she had not yet decided on her dissertation project; however, she was interested in how a particular gene (Dyrk1A) was involved in the generation of Tau, a protein that becomes "tangled" in Alzheimer's disease (AD).[99] In particular, she was thinking of focusing on whether particular ratios of two kinds of Tau, 3R and 4R, caused the behavioral phenomena associated with cognitive decline in Alzheimer's disease.

This was the first time Shui had presented papers as a part of the lab's journal club. Instead of circulating them via email the previous week, she had printed out copies for lab members and left them in their mailboxes before the weekend. This was unexpected, and several lab members did not know that this had happened, and the majority of those who had checked their mailboxes in time had forgotten to bring the printouts. That day, I sat next to Josefina who was not pleased about how much Shui had asked them to read before the meeting.

"I got through *one* of them!" She exclaimed, showing me her highlighted printout.

"What are they on?" I asked, not having a mailbox in the lab meant that I was unaware of what they would be discussing that day.

Josefina rolled her eyes saying that they were about "a bunch of different things."

For the sake of clarity, I will summarize what the papers were about, even though I figured this out slowly over the course of the discussion and after. Notably, the three papers used cell lines from three different living systems. One paper, which Josefina had read, used rat neurons to study how 3R-tau (a protein) comes to be overexpressed in cases where there are

[99] Tau is involved in maintaining the transport system in neurons; however, in the case of AD or AD-like pathology in DS, Tau proteins collapse. They become twisted into neurofibrillary tangles that prevent transport within neurons that is necessary for maintaining the health of the cell.

neurofibrillary tangles (Yin, et al., 2012). In this paper, the rat cells served as models of human AD. Another paper, which Shui spent surprisingly little time discussing, referred to DS mouse models to investigate how the overexpression of Dyrk1A and its relationship to learning and memory deficits. The last paper used cellular models of human DS to study abnormal tau expression in both human AD and DS (Cárdenas, et al., 2012). This paper, which Shui would refer to as having "human data," did not actually use human cells. Instead, it used Ts16 mouse neurons which were further modified to carry human Tau mutations. As with the Tc1 mouse described in the previous chapter, this paper used a mouse that was carrying human DNA in addition to mouse DNA.

Rather than explain and defend the findings of the article in her presentation, Shui tried to use the three papers to present an argument that was only possible if one accepted the findings from each article and synthesized them to support a claim that was not in any one of those papers. These papers focused on different processes that occurred at different biological levels, i.e. intracellular, intercellular, and behavioral, and each paper used a different organismic model. Her synthesis, however, produced a "textually compiled" model. By this phrase, I mean to capture how Shui took published data from different models and combined it together through speech to create a unified, albeit strictly conceptual, model. She admitted towards the end of the meeting that her intention was to present an argument why she should be allowed to conduct an expensive experiment which would require the lab to purchase new equipment.

She started with the paper using rat neurons as a model of AD. After presenting the methods and results of the paper, she said that this paper demonstrated that "the neurofibrillary tangles mean it is Alzheimer's. And it is the imbalance of 3R-tau and 4R-tau that cause the tangles." A senior scientist who had taken on a mentor role to Shui ("Ming") attempted to ask

her questions about the details of the case, but she moved to the second paper on mice. Those who had the printouts of the papers shuffled to find the second one, some began to skim it. The point that Shui wanted the lab members to focus on was that the DS mice that were modified to have an overexpression of Dyrk1A also had poor performance in learning and memory tasks. Furthermore, these mice performed worse than the same mice that were not genetically modified to produce this overexpression.

Ming began to ask Shui another question about the first paper using rat neurons, but Lawrence cut him off.

"Okay. So you have these three papers. Tell us why you wanted to present them."

"Well you know that Shui has been interested in longevity, and I think you could say that all of these papers have something to do with that," Ming said, coming to her defense.

"Sure, but is this about gene activation? This one (waving to the first paper) is about Tau. This one (waving towards the second paper) *is* about Dyrk1A activation," Lawrence said.

"I think both of them show that Dyrk1A, when it is overexpressed, does impact longevity," Shui said.

"What? Where does *this one* (pointing at the first paper) show that?" Lawrence asked.

"Well, it is about Tau," Shui replied."

Here Shui was displaying that she had been going beyond what was discussed in the first paper. The first paper did not mention Dyrk1A; however, there is evidence to suggest in other literature that the expression of Dyrk1A does affect the production of Tau proteins. Therefore, Shui's suggestion that because the paper is about Dyrk1A it has implications for Tau is not factually incorrect in the context of their field. However, Lawrence's confusion over how the first and second paper are both about Dyrk1A suggests that Shui reasoning is going beyond the

acceptable limits of inference-making. Shui is assuming that the Tau in the first paper is being affected by the behavior of Dyrk1A in the second paper. Although this may seem like a small inference to make, what enabled Shui to make this claim was that she treated the phenomena described in both papers as pertaining to a singular system. In this way, she was basing this perceived similarity on a textually compiled model that she constructed from the two papers.

"But how does this connect to longevity? If you want to talk about longevity, the longevity of a neuron. If you want to know what a cell is thinking, doing, going through and you ask individual neurons what is being enhanced. What are these young guys feeling? What are these old guys feeling? You can take part of the LC [locus coeruleus] in mice, use fresh tissue and ask them… 80% of the neurons die, but 20% are fine forever – they don't care!"

"Well I have some of the human data later which supports Dyrk1A regulating Tau expression–" Shui said while picking up the third paper.

"Yeah, but what do humans really tell us?" Lawrence said, cutting Shui off, "You can make a case for anything causing anything in a human. The mice are *really* important and this lab (pointing to the first paper) isn't using them."

It was then that Shui fully outlined the connection she saw between the three papers. She wanted to use the paper involving rats to establish that it was an imbalance of 3R and 4R-tau, where there is more 3R-tau, that causes neurofibrillary tangles in AD. She wanted to use the paper involving mice to show that there is a behavioral change when there is an over expression of Dyrk1A. The cells with human DNA would serve as a bridge between the AD rat model and the DS mouse model. This is because the cells containing human DNA were being used to make claims about both AD and DS cognition. Effectively, Shui was proposing a mechanism which would provide an organization of the parts and processes described in the papers she assigned for

that lab meeting. However, an assumption of this argument was that the processes described in the papers could occur within the same system. Shui's proposed mechanistic explanation was not an explanation of a mechanism in any one of the models used in the three papers. Instead, Shui's mechanistic explanation was of a textually compiled model she had constructed through conceptual reasoning. Figure 4.1 is my attempt to illustrate the parts and processes that Shui was arguing gave rise to the phenomenon of behavioral change. It is not properly mechanistic because it was unclear to me how she saw the parts and processes were causally organized. I have visually tagged which paper is providing data about the cellular parts under discussion.

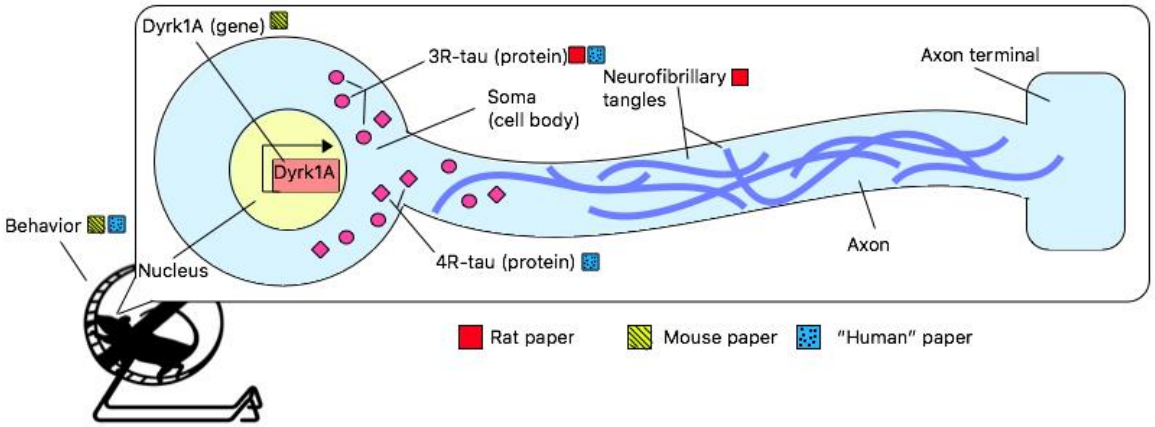

Figure 4.1 Shui's argument. The three papers that Shui presented focused on different cellular processes. Shui proposed an experiment which would show that these different parts and processes constituted a mechanism which would produce the phenomenon of impaired cognition associated with AD. The graphic depicts the parts under discussion and indicates which paper focused on which part.

As Shui explained it, she wanted to use the findings in the paper using human DNA as evidence that it is a Tau imbalance that causes the behavioral effects seen in the mouse model. In her argument, even though the first paper using rat neurons did not actually look at Dyrk1A, but a protein whose expression it affected, it is reasonable to infer, because of the human data, that there was an overexpression of that gene. With this inference, it is then reasonable to conclude

that if there is an overexpression of Dyrk1A in rats, these rats will have similar behavior to the mice in the second paper. Shui said she wanted to confirm that "the imbalance of 3R-tau and 4R-tau in mice results in behavioral symptoms." In addition to running behavioral tests, Shui wanted to precisely isolate 3R-tau and 4R-tau in a way that would require the lab purchasing a vacuum pump and compressor that would need to be vented outside.

However, as Lawrence asserted through his comment, human data is not well understood and is so complex that "anything can cause anything in a human." Additionally, neither rat nor human models are as important as the data which could come from mouse models. After Shui explained her reasoning, with many interjections from Lawrence and Ming, Lawrence gently dismissed her argument by finally saying, "these are three different models." This effectively dismissed the epistemic viability of Shui's inference. As Lawrence says, this is an issue because the phenomena described in these papers come from three different material models, which precludes assuming that the same kind of gene and protein expression is occurring in each system.

He continued by suggesting she run a less expensive experiment that would not require the lab to buy any new equipment. "This," he said, referring to his alternative experiment, "would not be a means of testing your hypothesis about there being a particular imbalance of 3R-tau and 4R-tau that causes neurofibrillary tangles. And whether these cause behavioral symptoms indicative of cognitive decline. They probably do! But it *would* allow you to determine whether decreased amounts of 4R-tau in *in vitro* DS mouse neurons caused cell death…. If this experiment shows that cells would die if there is an imbalance, which it probably will, but how it happens will be interesting. Does it take a long time? First give the culture some – it doesn't need to be precise, and then give it a lot, just to see what happens. If this works, we can discuss

seeing how we could run the experiment you envisioned. Or maybe we can see if another lab will do it!"

To make clear, the initial experiment that Lawrence proposed would not confirm Shui's mechanistic explanation; instead, it would offer additional details on 4R-tau's involvement in cell health and death. It would be additional work to determine whether cell death, if it occurred, resulted from neurofibrillary tangles in the neuron. The results from this experiment would fall far short of the mechanistic explanation Shui hoped to demonstrate as her dissertation project. Lawrence's suggestion carried the implication that her material intervention on DS mouse neurons had the potential to justify the costly experiment she envisioned.

This case reveals that a mechanistic explanation alone does *not* count as sufficient justification for devoting lab time and resources to undertake an expensive project in Lab X. As the philosophical literature concerned with biological practice articulates, and is born out in everyday science, biologists are concerned with providing mechanistic explanations (Wimsatt, 1972; Bechtel & Richardson, 1993/2010; Machamer, Darden, & Craver, 2000). A mechanism is articulated as a means of explaining how a phenomenon occurs. From what I have witnessed, Lab X regards mechanisms in a way that is accurately captured by how the New Mechanist literature has defined them, specifically Machamer, Darden, & Craver's expression of: "mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (2000, p. 3).[100] One of the goals of Lab X as an organization is to produce mechanistic explanations of disease phenomena, as is the goal of labs which have biomedical foci (Machamer, Darden, & Carver, 2000, p. 4). Shui seeking to provide a mechanistic explanation by compiling data from the three papers containing

[100] I am not claiming that Lab X endorses any of views in the New Mechanistic literature on the ontological status of mechanisms.

three different models does achieve the formal structure of the goal. In other words, Shui's justification for her project was in the form of a goal of Lab X, i.e. a mechanistic explanation; however, she disregarded or undervalued a standard which must be met in order for a mechanistic explanation to be credible.

Although Shui was good enough in the physical work of neurobiology that she had advanced to candidacy and was entrusted with doing a considerable amount of experimental work, she had not properly valued the epistemic role of materially working with models in this instance. Shui's lack of attention to how the experiential dimension mutually constitutes the conceptual in experimentation resulted in her exchange with Lawrence and Ming. In this discussion, Lawrence first expresses confusion regarding how Shui could think that both the first and second paper are both about Dyrk1A. Shui then explains that both papers are concerned with Dyrk1A because while one paper discussed it directly, the other discussed proteins that Dyrk1A affects, which she thinks implicates this gene. However, Lawrence continues to resist combining the results of the papers to make a claim about the longevity of a neuron.[101] He then offers a material means of studying the longevity of a neuron by saying, "If you want to talk about

[101] This is not to say that the senior lab members were against any inferences between mice and humans or between organisms. The entirety of the lab's research depends on their ability to make justifiable inferences between mice and humans. Cases where the lab members regarded their inferences as justifiable routinely involved meeting several requirements: 1) that the inference be based in a model that had a body of literature around it that supported its representational adequacy for human phenomena; 2) that the phenomena be discrete and measurable so that if there were a test conducted in human cells, it could be confirmed; 3) that it be produced in a biologically plausible way. This last point was often the most significant factor because much of Lab X's work would have required such invasive procedures on humans that they were ethically prohibited from doing so. To determine whether something would be biologically plausible, the lab members would investigate the way the model was produced. If it required electrical or chemical intervention, they would investigate whether these naturally occurred at the same level in humans. Additionally, they would investigate the structure of the model asking questions such as: would it be surrounded by the particular kinds of cells used in this experiment? Would there be other chemical factors around the cell that would amplify or suppress the phenomenon in which we are interested? The following chapter will also discuss how the biological plausibility of a given model would often be addressed through discursively "subjectifying" a model.

longevity, the longevity of a neuron… You can take part of the LC [locus coeruleus] in mice, use fresh tissue and ask them… 80% of the neurons die, but 20% are fine forever – they don't care!"

Through this exchange, Shui reveals that she did not yet have the same background expectations of how one ought to justify undertaking an experiment (Schutz, 1944). Although Shui was an advanced graduate student, she was still at the beginning of her career as a biologist. As is common among novices, she misinterpreted the task she had been assigned and used her own skills in logic and reasoning to fill in for the standards by which her work would be evaluated (Hellerman & Doehler, 2010). Lawrence's statements indicated what he thought was incorrect about her attempt at justification and revealed that proper justification would a) rely on *only* mouse data because "mice are *really* important" and b) be supported by Shui conducting either her own experiment or confirming the results in one of the papers in a way that would allow the rest of the lab to discursively construct what materially would need to be in place for her mechanism to be plausible.

A key difference between how Lawrence and Shui evaluated whether her textually compiled model was sufficient justification for her proposed experiment was how they treated the relationship between the embodied experiential dimensions of practice and the conceptual. An example of this was the different degrees of priority they gave to the material history of models. For Shui, her textually compiled model was sufficient because it enabled her to provide a mechanistic explanation, which is the ideal form of a justification in their field. She did not demonstrate concern over the fact that the processes she was positing as parts of her proposed mechanism were from entirely different organisms. It appeared she was chiefly concerned with the conceptual form of the justification she was offering. For her, a mechanism seemed to be a formal structure that would explain the particular result she hoped to get.

Lawrence, on the other hand, was careful to index the specific parts and processes to the particular papers in which they were described. For instance, he was clear that the first paper, which used rats, was about Tau and the second, which used mice, was about Dyrk1A. Despite whatever relationship Dyrk1A and Tau might have in any system, Lawrence refused to make the move Shui did and regard them as describing related processes in the same model. Lawrence rejected Shui's textually compiled model and, instead, asserted that "these are three different models." In other words, he did not think that the lab could discursively bring the findings from the three papers together to justifiably construct the model Shui was proposing. In their study of a novice performing an experiment under the instruction scientist, Lynch, Livingston, and Garfinkel come to a similar conclusion about the significance of the material work of experimentation (1983). In their case, they found that neither the embodied work of experimentation was fundamentally different than the instructions for it or descriptions of it. Instead, these inscriptions were indexed to the practice in which was located the "knowledge" of, and produced by, the novice. Likewise, in my case, I contend that Lawrence rejected Shui's textually compiled model because it was abstract without any grounding in a particular kind of living system. Furthermore, there was no concrete system in which her proposed model had ever occurred either in their lab or in a published study.

The standard that emerges for evaluating one's model demands one of two things. A practitioner must have produced it and provided enough information about their embodied process through methods that Lab X affirms are correct. Alternatively, a practitioner can discursively reconstruct an experiment or construct one in a way that lab members agree is biological plausible. Furthermore, the experimental work that produced the model or data must be grounded in common and epistemically meaningful procedures. This standard emerged fully

when Lawrence gave Shui an option for justifying her proposed project. She could have run a coarse-grained experiment which would have shed light on how long it takes decreased amounts of 4R-tau to cause cell death. Significantly, in order to do this experiment, she would have had to prepare a culture in the manner that 4.3 instructs. The data Shui generated would, thus, attain a degree of epistemic rigor through the foundational embodied work she would have performed to produce her model.

This standard as it emerges through this case reinforces an interpretation of the instructions in 4.3 that views the conceptual and experiential mutually constitutive and enables practitioners to produce a model that has the capacity for justifiable representation. This is revealed through Shui breaching a norm in the lab of contextualizing the material source of data. Instead of specifying that the Dyrk1A she had data on was from mice, or "mouse Dyrk1A," she treated Dyrk1A as a general category, which she also did with "3R-tau" and "4R-tau." Because she decontextualized the data on these objects from the three different cellular models, she was able to combine them together to produce a general model of a neuron. However, for Lawrence, and the other senior members of Lab X, it does not make sense to talk about Dyrk1A in general. It must be specified in a particular system. An unqualified neuron is an equally non-meaningful object. The neural models that Lab X uses are explicitly "mouse models" because it was a large achievement of the field to be able to justifiably decide that there is similarity between neurons from certain transgenic mice and humans with DS or AD. Because Shui brought together decontextualized data from multiple animals to offer a mechanistic explanation that does not occur in a *particular* system, she overgeneralized to the point where she did not have a model that could justifiably represent any target phenomena. I argue that the specific way in which Lawrence expressed confusion over Shui's proposal supports the interpretation that in this lab,

and their field, these concepts of, for example, “Dyrk1A” and “Tau” are indexed to a history of embodied actions engaging with particular kinds of biological material. The experiential work is interwoven with, and grounds, these categories used to specify classes of objects (Wittgenstein, 2009; Lindwall & Ekstrom, 2012). The categories of “Dyrk1A” and “Tau” offer a shorthand to give meaning to the particular objects which fall under them. This is also present in the instructions which deploy concepts such as, “hippocampus” and “magnesium sulfate” which are only meaningful because of numerous practitioners interacting with these kinds of objects in particular ways for specific purposes. It is the physical actions of the practitioner involving these objects which reestablish the meaning of these categories which were born through a history of other practitioners engaging in the same activity.

Furthermore, this case reveals the significance of communication’s role in evaluating a model. In this meeting, the activity of conversing simultaneously was the context in which the lab members were training each other and the means by which they were attempting to construct the materiality of Shui’s proposed model. In this way, the lab members use their meetings (which are just long conversations) to justify their epistemic work as well as bring newcomers into their field.

4.6 Conclusion

This chapter attempted to accomplish two objectives. First, I sought to show how lab members train novices to see how the conceptual and experiential come together in experimentation. When the senior members train the newcomers to approach lab work in this way, the junior members learn both how material practice has epistemic significance in the lab and how to be members of the lab’s community of practice. My second aim was to show how

the physicality and sociality of experimentation enable the lab to make justified epistemic claims. In the first case (4.4) I showed how epistemic achievements are predicated upon the social and material interactions in the lab. In the second case (4.5), I revealed how a model's epistemic significance is dependent upon the ability of the lab members to collaboratively reconstruct the material interventions that took place in experimentation. By exploring how Lab X trains its students to conduct these aspects of everyday biological practice, I have uncovered how the lab members break down the dichotomy between the conceptual and experiential in material and discursive practice. Through describing how they do this, it is possible to see the epistemic significance they give to their collaborative efforts to physically and discursively construct and reconstruct models when evaluating or designing experiments. I contend that the foundational standard that is related to this valuation can be found in the instructions of the most basic and mundane procedure the lab uses on a daily basis (4.3).

This initial norm that comes from these instructions is that a model's adequacy is grounded in the doing of the material interventions which produced the model – not in an *a priori* or *ex post facto* determination (4.3). Through the enactment of a model, the traditional dichotomy between the embodied experiential and the conceptual dissolves. Studying this procedure as it is textually described and how it is taught and deployed in practice reveals that mutually constitutive relationship of the experiential and conceptual affords a model's epistemic adequacy. In the context of learning how to conduct a mouse sacrifice and hippocampal dissection, it is clear that internalizing the steps of this procedure is insufficient for learning in this lab. Instead, the standard for learning the procedure parallels the interwoven nature of the experiential and conceptual in the procedure itself. A student must know the steps and be able to perform the physical task, but they must also value the significance of the steps of the procedure

in terms of how they relate to: the finished model, the smooth functioning of the lab, and producing material with which other lab members can work. Learning this procedure involves coming to see oneself and one's activities as part of the community of practice that is the lab (4.4). Lab X's standard for evaluating one's own model is that one must have actually made the model through a common procedure of which one's lab and greater community recognize its epistemic significance. Alternatively, if someone in the lab did not physically make the model, it can only be a justifiable representation of human phenomena if they are able to discursively construct or reconstruct it, after which its biological plausibility can be evaluated (4.5).

In both of these cases, the epistemic significance of the Lab X's work stems from a dissolution of the traditional dichotomy of the conceptual and experiential, the mental and the physical, or internal understanding and external doing (Lave and Wenger, 1991). Unsurprisingly, the standards for making or evaluating models emerge most visibly in instances of training. However, the training is not separate from the epistemic accomplishments of the lab. Because the members of the lab teach junior members by incorporating them gradually into their community of practice, the newcomers participate in the lab's epistemic accomplishments *and* in maintaining its standards for these accomplishments. Producing knowledge claims in Lab X is inseparable from the communicative activity that the lab members perform both materially and discursively.

Chapter 5

Subjectification in Modeling Practice

5.1 Introduction

This chapter focuses on what Lab X's practices of training its junior members reveals about its standards for objectivity and its methods for meeting them. While taking a phenomenological approach, I will engage with literature in STS on training graduate students and the roles of subjectivity and objectivity in science. I will also speak to related debates in the philosophy of science. I will argue that by following the concerns biologists have regarding how they train their students, one can gain insight into what objectivity means to them and their standards for achieving it. When referring to objectivity outside of how Lab X means it, I am not drawing on any thorough account of the term. Instead, I mean the common, everyday meaning of the word which connotes something like "the way things are" or "what is actually in the world." The "world" that the lab members are trying to make claims about is typically outside of their lab – the world of human disease at a cellular level. They do this by bringing in pieces of this world through their mouse, which have been genetically modified so that their cells behave the way those in human conditions do.

As I will show in the following sections, while Lab X is committed to making claims about how the world is, how they go about making these claims is striking. The lab members frequently use subjectifying language when speaking of the biological material involved in their experimentation. When I use the word "subjectifying," I am drawing on Foucault's work which

describes how a "subject" is produced through multiple kinds of discursive, physical, and institutional practices (1982, p. 777). To "subjectify" is to constitute something as a subject that has awareness and a kind of personality.

In the cases I present, the lab members constitute neurons, receptors, and mice as subjects that have their own preferences, reasons, and motivations for their activities. As I will show, the biologists in this lab use this kind of language when pursuing two kinds of objectives. The first is to investigate alternative accounts for what caused a biological process. The second is to cede epistemic authority to the biological objects as part of the lab's pursuit of objectivity. For the lab members, what counts as objective is not some piece of information that is ungrounded from a perspective. Instead, "objective" information in Lab X consist of the "feelings" and preferences of a neuron, for example, about its own nature. While this discursive practice certainly does not appear in the papers they publish, it is present in the lab members' collaborative design or assessment of an experiment.

When pressed about why they use this kind of language, as I will show, they report that this is "just a thing we say." However, I argue that this language use is essential to their practice of training students to adopt a specific perspective when assessing an experiment. I also argue that this language is crucial for them performing the activity of assessing the merits of an experiment, not just in the context of training novices in this skill. I contend that the lab members' standards for assessing the objectivity of an experiment requires them to constitute biological objects as subjects.

Not only do they constitute mice and neurons as subjects, they also constitute them as types. By constituting these biological objects as both subjects and types, the lab members cede to them epistemic authority over the disease phenomena the practitioners are modeling. By using

the term "type," I am drawing from Schutz's early phenomenological work on sociality. He was inspired by Weber's conception of "ideal types" and described how in our everyday experiences, people frequently posit the concrete existence of an other without positing a specific person. One such example would be when one buys fruit from the grocery store. A farmer grew it and a farmworker picked it, but one draws on a general idea of "a farmer" or "farmworker" when one posits the necessary concrete existence of that person. In Lab X, the lab members constitute biological material in a similar way, where they posit the existence of a singular entity to refer to the many such objects that were used in a particular experiment. For example, the lab members will refer to a process in "the neuron" even though they are referring to the average of that process that occurred in the thousands of neurons they studied. In their discussions, the lab members typify the objects they constitute as subjects which enables the lab members to generalize their findings to apply to multiple neurons in their lab and outside of the lab, either in the "real" world or in other labs.

By using these two methods of subjectification and typification, I offer an account of what objectivity is for a group of scientists. Additionally, I reveal that in their everyday epistemic work, the lab members locate objective information in materiality and in a perspective other than their own. The lab members' approach to producing objective claims affects their focus in their design and assessment of experiments. Specifically, I show that their collaborative discursive work is not explicitly devoted to making claims about what is out in the world, but what is true for the material they constitute as subjects. Their conversations about how to get at what is true for these biological subjects center around determining the justifiability of their methods and approaches of inquiring into this truth. By revealing the lab's practices of meeting

their standards for objectivity, I hope to add the experiences of scientists into discussions in STS on the role of subjectivity and objectivity in science.

Additionally, I intend to challenge traditional approaches within the philosophy of science that draw clear lines between realism and constructivism. Traditional scientific realism endorses the reality which is described by the best available scientific theories. Constructivism, on the other hand, emphasizes that what one regards as "reality" is constructed through cultures or conventions, perspectives and experiences, and actors with their own biases and beliefs. I want to show that Lab X's means of obtaining objectivity do not fall neatly into either camp and, instead, break down this dichotomy. As I will demonstrate, for the lab members, the neurons they study are real objects that are the site of inquiry. Furthermore, *the neurons* are the ones that are offering their perspective on themselves and *this* is regarded as the highest epistemic authority when assessing an experiment. This raises a question about whether subjectifying is metaphysically real or if it is a heuristic, as an instrumentalist account would suggest. When contextualizing this question within my phenomenological approach to studying scientific practice, it appears that my approach would support either a realist or instrumentalist/constructivist account. However, I would argue that a phenomenology of scientific practice is compatible with both and reveals how both are important for understanding Lab X's practices for determining objectivity.

In 5.2, I will review how scholars in the humanities and social sciences have approached questions about objectivity and subjectivity in science. Then (5.2.1) I will discuss related concerns in the philosophy of science regarding realist approaches to science and their tensions with instrumentalist or constructivist accounts. I will also (5.2.2) discuss how STS practitioner have studied scientific training and their foci of study. I will next (5.3) describe the theoretical

interventions I am making in this chapter. As described earlier in Chapter 1, I am using categories of analysis that are not those that the members of Lab X use. While I do so as part of working at the epistemic level of analysis, I also do so to communicate the significance I found in the phenomena I witnessed to an audience beyond that of biology. I will then present three cases that I will analyze through the conceptual tools I describe in 5.3. The first (5.4) will revisit Shui's initial project proposal described in the previous chapter; the second (5.5) will focus on the lab members speak of their mice; and the third (5.6) will present Shui's second attempt to propose a project to the lab. The final section (5.7) will describe how my analyses contribute to discussions in STS on objectivity. It will also describe a new approach to studying objectivity in science that give voice to the experiences of its practitioners.

5.2 Literature

In science studies, there has been ongoing interest in questions concerning the objectivity of science. These questions emerge out of the commitment to treating scientific and technological work as inherently social (Bloor, 1981). If science is social, how could it attain the epistemic status of objectivity? What does objectivity even mean if it is produced through fundamentally social practices? This section outlines literature in STS and texts that have been important to social studies of science on the topic of objectivity. The presentation here is informed by my own interests in how subjectivity enters scientific activity as well as how practitioners, of both STS and science, negotiate the difficulty of undertaking any effort that meets the high standards of their discipline.

The cases I describe in 5.3 and 5.5 capture two core difficulties that graduate students face when training in Lab X. First, they must learn what "life as usual" is like in the lab (Garfinkel, 167, p. 37). By this I mean that they are expected to pick up the expectations the lab members have for how to present and analyze data, protocols for benchwork, asking for help, etc. While some of these are shared in their field, many are unique to the lab and its members. The second difficulty that graduate students face is that their object of study, age-related cognitive-impairment in Alzheimer's disease (AD), is not defined by a clear cause. Additionally, how Lab X, and the field of neurobiology, characterize AD is seemingly at odds with how the lab seeks to understand the disease.[102] As Moreira, May, and Bond articulate, in the early days of neurobiology studying AD in the 1970s, there were competing theories over what the cause could be (2009). For example, there was debate over whether AD was caused by toxins, a virus, or a neurochemical imbalance. In fact, there is still dispute over these same possible causes. While pursuing these different lines of inquiry, neurobiologists systematically documented the disease at the level of behavior (Moreira, May, & Bond, 2009, pp. 668). The history of research on AD has led to a particular conception of the disease as one that is defined by behavioral symptoms first and foremost.[103] For instance, memory loss, confusion, and depersonalization are all regarded as defining characteristics of AD.[104] Biologists agree that the Amyloid plaques and neurofibrillary tangles associated with the condition are responsible for the behavioral changes. Yet, because these plaques and tangles can occur in Huntington's disease and Parkinson's

[102] As the next section shows, Shui grapples with how to prioritize both the field's prioritization of behavior as the defining feature of AD and her lab's concern with activity at the molecular level.
[103] This is not dissimilar to Fleck's account of how a disease entity becomes crystallized over time through the course of research and enmeshed in the sociohistorical context in which it occurs (2012).
[104] Notably, Alzheimer's disease cannot be definitively diagnosed until after death by performing an autopsy to ascertain the presence of Amyloid plaques. While other dementing conditions can be ruled out, there is not a positive test for AD. In this way, there is similarity to Fleck's account of Syphilis before the Wasserman reaction provided a means of distinguishing it from other sexually transmitted diseases.

disease, the presence of these traits alone does not signify AD. Because of this, even Lab X, an organization which is concerned with the genetic and molecular causes of AD, must justify its work at the molecular level with respect to the behavioral phenomena. As I will show, there is a parallel between the field's tendency to characterize AD in terms of behavioral symptoms and Lab X's own practice of using personalistic or subjectifying language when referring to their mouse models, especially their neurons.

STS has also provided accounts of how subjectivity and intersubjectivity figure in scientific work. Some accounts have focused on how scientists "see" the objects they use in the course of their activities. Maynard and Schaeffer trace interests in STS on the roles that subjectivity and objectivity play in science to the phenomenological tradition (2000). "Husserl's phenomenology aimed at ultimate clarification and justification of both theoretical and empirical knowledge, which he saw to be grounded in *scientists'* pre-theoretical and pre-hypothetical forms of knowing" (Maynard & Schaeffer, 2000, pp. 335). Referencing Husserl's *Crisis of the European Sciences and Transcendental Phenomenology*, Maynard and Schaeffer are describing Husserl's distinction between how scientists know objects in, and through, their everyday lived experiences, and how they know these objects empirically. For Husserl, this empirical understanding is grounded in the pre-scientific subjective experience of objects. A task in science is to transform that object of experience into something that is "intersubjectively determinable, and communicable in its determinations, for everyone" (Husserl, 1970, pp. 23, 27). Or at least for everyone who has been trained to understand how a given scientific field makes things determinable and definite, e.g. in formulas and data graphics. This idea that scientific "objectivity is intersubjectivity" is echoed by Rorty (1987, p. 41-42) as well as Shapin's discussion of how viniculturists can come to an "objective" agreement about taste (2001, p.

176).[105] I position my discussion in the context of these authors who are committed to the "pre-theoretical and pre-hypothetical" form of knowing as foundational for whatever one considers to be proper "scientific" knowledge.

Another approach STS has taken is to study how practitioners' own uncertainties and individual acts of interpretation and synthesis shape understandings of objects in science (Hogle, 2009).[106] This orientation treats the concept of "subjectivity" as the personal preferences, biases, human affairs, or constitutive activities of scientists that enter into and produce their objects of study. In these accounts, the objects under investigation push back and interact with researchers in particular ways in particular contexts. The concern about subjectivity in these discussions is not about the Being of objects of science, but the practices surrounding these objects in their individuality and situatedness.

This has the formal structure of Heidegger's concept of "*existenziell*" which refers the "everydayness" or public facts of some particular being or object. These accounts are not focused on the ontological-*existenzial* structures of an object, which would be investigations of their existence (Heidegger, 1996, p.12). An object, such as a disease entity, can be characterized in different and sometimes contradictory ways across multiple areas of practice. This is because of the unique and specific methods and theories involved in the different sites in which, what is thought to be the same disease exists (e.g. the clinic, a research lab, one's own body) (Mol, 2002). This multiplicity destabilizes a disease entity as a unified object (Singleton, 1998). This is particularly evident in undetermined cases where the descriptions of a disease entity do not create boundaries that pick out just one condition (Rabeharisoa & Bourret, 2009). As I stated

[105] See also Shapin's (2016) further account of how subjectivity is essential in wine-making because of the value the profession places on "taste."
[106] The "objects" can be material or conceptual.

earlier, this is the case with AD. Yet even though the subjective aspects of scientific work can cause that with which it engages to have unstable identities, this same work can bring together the multiple identities associated with a given object (Riles, 2006) For example, shared protocols and guidelines can make conceptions of a disease entity cohere across different domains of practice. Examples of this are titer tests used in a clinic to ascertain whether someone has contracted a disease or in a laboratory where researchers try to determine whether a vaccine was successful in preventing the contraction of that illness in mice (Hogle, 2009).

Another approach to investigating the role of subjectivity in scientific practice has been to focus on how the objects themselves become subjective. Some studies, such as Anderson's historical account of Kuru, have described how objects are produced by intersubjective collaboration and how this becomes a part of the material work (2012). In this case, Anderson shows how the relationships formed between those who had contracted Kuru and those researching it made it possible for the scientists to produce human tissue samples of the disease. Additionally, the social relationships which afforded the researchers the opportunity to acquire these samples was so central to the enterprise that, Anderson argues, "the value of the social relation became ever more absorbed in the material", i.e. the tissue samples (2012, p. 567). Others have made a stronger claim arguing that the material and discursive work with biological bodies turns the material into "material-semiotic actor[s]" and not just matter that carries the trace of the people which produced it (Prins, 1995, p. 355).[107] In this stronger approach "subjectivity" refers to the kind of Being that those involved in scientific endeavors have, which includes both human and non-human actors, including what are traditionally regarded as inert objects.

[107] Referencing Haraway's discussions of objectivity (1988; 1991).

The formal structure of Heidegger's concept of *existenzial* is useful here for understanding how these investigations in STS are concerned with the Being of things called scientific objects. Through Lab X's subjectifying work, the practitioners aim to communicate with their living models and "speak for" them in publications, which transforms them back into objects (Haraway, 1991). However, during their pre-hypothetical work, they inquire into the Being of the subjects which they constitute. Significantly, they do so by intentionally asking the biological material questions which it will answer by revealing its thoughts and feelings about its own nature.

However, while much work in STS is committed to subjectivity being involved in the production of scientific objectivity, there is little work on how scientists understand, and what they could mean by, "objectivity." Haraway describes one conception of objectivity as a disembodied and infinite view on how things are (1988, p. 575). Furthermore, those who make a claim to objectivity are carrying out "the god trick" which sees everything from nowhere (Haraway, 1988, p. 581). Haraway attributes this view of objectivity to an imagined "they" developed by social constructionists or non-scientists (1988, p. 576). Yet, throughout her argument for a notion of objectivity that is partial and situated, the voices of scientists are not present. Would they agree with her core contention that knowledge is from an embodied perspective that is always partial and local? Does an object of knowledge ever emerge as a "material-semiotic actor" for them in the course of scientific practice (Haraway, 1988, 1990; Prins, 1995)? One answer to these questions could be "no, otherwise why would one offer this feminist version of objectivity?"

Subsequent work in STS and feminist STS has provided accounts of how technologies and scientific products erase the everyday uncertainties and practices involved in their use or

creation. Beaulieu's discussion of neuroinformatics and NASA images (2001) and Hogle's on organ donation (1995) reveal how objects in science must lose their local meaning so that they can become standardized objective statements about reality. Other work has described how this erasure involves intentionally disinterested, aperspectival claims about the "really real" (Daston, 1992, p. 579). Furthermore, the process of determining what is *really* real is a moral one that determines the normal from the abnormal (Daston & Galison, 1992). Granting the accuracy of these accounts, which certainly track with the products and results of science, there remains the question of how those who produce these objects of science regard objectivity. Do they, in practice, marginalize and deny the status of "knowing and moral subjects" to those which are normally put into the position of objects? (Prins, 1995, p. 356-357).

5.2.1 Scientific Realism, Instrumentalism, and Constructivism

Most philosophers of science do not subscribe to STS's general commitment to science as a fundamentally social activity. While they would not reject that the pursuit of science is an endeavor with social aspects, the products of science are not themselves social achievements. For a realist philosopher of science, science gets to some kind of reality. How close science gets to a mind-independent reality is a matter of debate. Some philosophers, such as the New Mechanists, have grappled with this question in relation to explanations in science. They have contended that explanations of mechanisms are the structures in the world that explain a given phenomenon (Craver, 2014; Salmon, 1989/2006; Sheredos, 2016; Strevens, 2008). Others, such as Bechtel, are committed to some kind of world, but view scientific explanation as "through-and-through an epistemic practice of making the world more intelligible…" (2007, p. 51). And others see the

possibility of reconciling these two accounts of explanation while showing how science provides knowledge about a real, mind-independent world (Illari, 2013; van Eck, 2015).

In discussions about scientific realism itself, it is generally accepted that this kind of realism is a commitment to the reality of what the current best scientific theories describe. However, there are differences in what people regard as the correct relationship between scientific theories and truth. Some define realism as the successful reference of these theories to things in the world. Others see scientific theories, or parts of them, only approximating truth. For those who argue for scientific theories approximating or aiming at truth, they point to the aspirational nature of science as being sufficient for a realist stance (e.g. van Fraassen, 1980). In other words, scientific practice seeks to make true claims about a mind-independent world. Others regard this stance as insufficient for a proper characterization of scientific realism (e.g. Charkavartty, 2007; Kitcher, 1995). This is because while they acknowledge that scientific practices are real and aim at truth, they want a way of distinguishing successful and unsuccessful scientific practice. To do this, they also need a commitment to science doing more than aiming at truth, science needs to *obtain* truth in a way that is confirmable.

These conceptions of scientific realism stand in contrast with constructivist approaches to science. Philosophers of science characterize constructivism with reference to canonical texts in science studies. Drawing on Kuhn, some analytic philosophers of science associate constructivism with work that emphasizes a causal role of forces which are not agents, such as cultures or institutions in producing a phenomenon (1962). Others view constructivism as emphasizing the roles of people's biases, judgments, preferences, habits, etc. in the construction scientific claims (e.g. Pickering, 1984). An analyst using either of these conceptions of constructivism would see human actors or their human-oriented creations as having a causal

relationship to the production of a scientific claim. In these accounts, the "reality" of the world is produced through interactions between human actors and impersonal forces such as culture. Science, according to some accounts, does not get at a mind-independent natural world, but participates in the construction of the social world.

However, I would argue that contemporary biological practice reveals that neither a traditional realist or constructivist stance provide a sufficient account of how practitioners go about determining the objectivity, or reality, of a claim. As I will show, the members of Lab X discursively constitute (what they see as) real biological objects as subjects that have the authority to make claims about who they are and what they are experiencing.[108]

5.2.2 Training Students and Methodological Perspective

The lab members reveal the significance of discursive subjectification most often when training graduate students. When teaching their students to assess an experiment and design their own, they demonstrate how their practices of subjectification organize their epistemic activities. In this subsection, I will contextualize my approach to studying Lab X's practices of training within STS literature on science pedagogy. Additionally, I will lay the theoretical groundwork for making the claim that when the students in the lab are learning to subjectify biological

[108] One could take one variety of an instrumentalist approach and argue that this sort of activity is actually just a useful tool. Within this framework, the discussions in which lab members cede authority to the subjectified neurons, this would be a kind of anthropomorphization that is helpful for doing future scientific work that makes the world intelligible. However, if this subjectification is merely an instrument, it does not have any relation to the truth of how the world actually is. My argument is not that the members of Lab X constitute their biological objects as subjects merely as an instrument which they use on their way to making proper claims about the world. Arguing why I believe an instrumentalist account is insufficient for providing an adequate account of Lab X's practices is outside the scope of this chapter. However, one reason why I believe it fails to capture the phenomena I am describing is the following: The lab members do not treat their practice as a tool that does not have a relationship with a (human) mind-independent world. These biologists speak of the subjectified neurons as being able to report on their own nature. It is this report which provides a standard that organizes the epistemic work of the lab members.

objects, their supervisors are also disciplining the students as certain kinds of subjects. While the students are learning to subjectify neurons to give these objects epistemic authority, they are also undergoing a "disciplining" process that will give *them* the authority to speak as professional scientists.

There is precedent in STS for studying novice scientists, specifically graduate students. Most of these accounts have used interviews with graduate students and their supervisors as the primary source of data. Some have focused on how students learn the difficult skill of reading graphics (Bowen, Roth, & McGinn, 1999). These studies have focused on science education from elementary school to college, so they are less focused on the locality of particular reading practices. They also characterized proficiency in reading graphics by students' abilities to offer linguistic descriptions to characterize the meanings of a graphic. Others have revealed the challenge scientists-in-training have getting equipment, and overall projects, to work and how they come to accept this as a feature of the profession (Delamont & Atkinson, 2001). These studies have addressed the more traditionally "social" aspects of becoming a member of a profession by describing how students come to accept that getting "correct" results is never guaranteed. Additionally, part of becoming a member of the profession is being able to assess whether a project is likely to succeed and choosing a successful one as one's dissertation work. There has also been similar work that has focused on how students receive training, more generally, to become members of their fields' communities (Campbell, 2003). These studies have shown that science education at the graduate level is not rigid or characterizable through a pre-given set of rules. Instead, it occurs through formal and informal interactions with more advanced graduate students and faculty. Campbell argues that the real education graduate students in the sciences receive is through doing what fully trained scientists do (2002, p. 906).

Furthermore, by studying the activities involved in managing and training graduate students, one is able to understand the everyday work of science (Campbell, 2002, pp. 889).

While my overall orientation is most like ethnomethodologically-inspired studies of science, my discussion here intersects in aims with this last topic. That is, I am most interested in what instruction in Lab X reveals about the lab's everyday work – not just the features of the lab's organizational structure, but the work they do to make claims about the natural world and their standards for making these claims. However, while I align my discussion here with Campbell's scope of research, I intentionally am relying primarily on ethnographic data documented in the form of field notes and audio recordings as opposed to formal interviews. My motivation for basing my discussion on everyday conversation in Lab X's meetings is grounded in the phenomenological tradition as taken up by sociology. Since my interest is in Lab X's standards for objectivity as they emerge in the course of their everyday talk and action, it was more accurate to produce records of this activity as opposed to having lab members report on what occurred in their ordinary conversations.

Specifically, I am further drawing on the corpus of Alfred Schutz to distinguishes between the kind of meaning that methodologies construct. In this case, I am going to extend Schutz's conceptions of "understandings" to articulate what sort of meaning is constituted through analyzing *in situ* conversations and responses to interview questions. Schutz distinguishes the two ways of inquiring into the meaning that others habitually attribute to their activities as "observational understanding" and "motivational understanding" (1967, p. 30).

Pursuit of an observational understanding asks what participants are attempting to accomplish by undertaking certain actions. One arrives at an observational understanding of another's activities by watching them and reflecting on the connections between the other's

speech, bodily comportment, and activities with others and the world around them. Schutz presents the examples of a person using an axe to chop wood. By observing someone using an axe to chop wood, one achieves an understanding that that person is wielding an axe for the purpose of chopping wood. This sort of understanding does not make claims about any interior or non-immediately apparent meaning the other person may have in that moment.

This is in contrast with motivational understanding which enquires into what specific past events produced a current state of affairs. Generally, this involves asking a person after the fact why they were, for instance, chopping wood. They may answer that they were doing so because they work for a lumber company or that this was part of how they earn a paycheck (Schutz, 1967, p. 30). This introduces meaning that was not readily apparent if one were to have merely viewed the woodcutter chopping wood. However, asking the woodcutter to report on the purpose of their work after the fact does *not* reveal whatever meaning the act held for them during their performance of the activity. This, I see, is parallel is structure to the kind of understanding one achieves through conducting interviews. My interest is in what participants reveal about their understandings of, and standards for, objectivity in the course of discussions and not in how, or what, they would report about their own actions after the fact. Because of this, I have chosen not to base my analysis on interview data.

I will primarily pursue an observational understanding of what is happening in the cases below. *However,* as we will see, the lab members themselves are very much pursuing a kind of motivational understanding when they subjectify their mice and neurons. They explicitly want to ask what their neurons are feeling and why they did certain things in an experiment. Because my lab members are attempting to obtain a motivational understanding, I make a parallel attempt to describe how they are performing this pursuit of understanding. While attempting to study these

matters of concern from the levels of observation and motivation, I aim to provide a taxonomy of the kinds of subjectivity as they are constituted through practice. Additionally, I seek to provide an analysis of how the lab values these particular kinds of subjectivity and how they are made relevant in cases where the lab is concerned with what is ordinarily regarded as objectivity.

Even though I am focused on what Lab X's practices of training their students reveals about their own standards for achieving objectivity, I am still committed to studying their matters of concern. A chief concern in all these cases is educating the novices in the lab. In the instances where the students are learning to subjectify biological material, they are also being disciplined into a particular kind of subject. These are different kinds of activities, even though they occur simultaneously in practice. They are different because the professional subjectification the novices undergo is intended to continue past the subjectifying interactions which occur during their training. This is in contrast with the subjectification of the neurons under discussion which are only constituted as subjects during the lab members' work to design and access experiments. After these activities end, the lab members no longer speak of the neurons as subjects. The students, on the other hand, still retain their status as subjects who are undergoing professionalization.

Foucault's account of the subject captures the more metaphysical nature of the lab's work to turn its students into a certain kind of subject. Foucault's subject does not have the *a priori* status of Husserl's pure ego. Instead, Foucault's subject is produced through "dividing practices" which either render a subject distinct from others or divided from its own self (Foucault, 1982, p. 777). "Some of these individualizing practices are discursive… others are institutional" and occur in the context of history and culture (Olssen 1999, p. 31). In *Discipline and Punish*, Foucault provides a brief taxonomy of the areas of the soul that others have studied. In addition

to the psyche, consciousness, and personality, "subjectivity" has also been distinguished as a topic of inquiry (Foucault, 1977, p. 29). Foucault refers to the phenomenon in which all of these areas have been defined as the soul, which is produced through "punishment, supervision, and constraint" (1977, p. 29). Because Foucault refers most to this phenomenon not as a soul, but as "the subject," "subjectification," and "subjectivity," I will do the same. He does not give a description of the nature of the subject, or the soul, but instead focuses on how it is produced through practices which exert power and impose constraints on others. However, because he places understandings of the psyche, personality, and consciousness as aspects of the subject, it follows that the Foucauldian subject has these features. Significantly, though, they cannot exist prior to interactions that are shaping, limiting, or evaluating.

The idea that features such as a personality or interiority are produced through multi-modal practices is helpful for seeing how Lab X's training practices are intended to produce a certain kind of professional subjectivity. In the following sections I will *not* claim that this sort of metaphysical constitution is occurring when the lab subjectifies its experimental material. However, I would like to flag that these disciplinary practices are occurring throughout the lab's efforts to train their students to "properly" assess experiments. Instead, I will focus on how the lab members actions constitute the models as subjects in the context of particular interactions. I will argue that these subjectifying activities are a meaningful part of how the lab members assert their standards for objectivity while also holding themselves to these standards.

5.3 Theoretical Interventions

My account of Lab X's practices of assessing the objectivity of experiments and their own efforts to meet their standards contains some of the tensions that are apparent in the realist/constructivist discussions in the philosophy of science. One of the core tensions which resonates in my cases is whether the products of science, such as facts about the world, are discovered as structures in the world or if they are social constructions that are only meaningful to the social actors who produce them. However, by taking a phenomenological approach to the lab meetings which I have observed, neither the realist nor the constructivist approach is adequate for describing the lab's epistemic practices. The lab members are committed to the biological objects being real structures in the world, whose internal processes. However, they also subjectify the biological material and specifically describe the importance of asking it questions about what it is thinking and feeling. Yet, this does not seem to be a straightforward case of constructivism. This is because, once subjectified, the material the lab members work with gains the authority to answer questions about the material processes occurring within it. Furthermore, *how*, and the context in which, the material answers is taken as the standard by which to assess the plausibility of the material as a model. In other words, the way in which the subjectified material communicates determines whether the lab members deem it an adequate representation of the world outside of the lab.

This discussion does not rely solely on the categories that the practitioners explicitly use in their conversation. As described above in reference to Schutz, I am interested in understandings of objectivity and subjectivity that are displayed through practice. The members of Lab X did not use this language in their conversations. This is, perhaps, because explicit interest in these concepts is more common in disciplines that study and use these concepts in the course of their own knowledge producing practices. Continuing to engage with Wittgenstein's

concept of "language games," while designing an experiment, the neurobiologists operate within the boundaries of their discipline, complete with the agreed upon terms, their meanings, and coordinated actions. Much like Wittgenstein's builders, the members of Lab X use their disciplinary-specific language to accomplish their goals (2009, p. 8). A word itself is not inherently meaningful without a speaker drawing attention to its significance such as by defining a word (e.g. "by 'slab,' I mean…"), assigning a word to an object,[109] offering a pronunciation of the word (e.g. "pronounce the word 'the'")[110], or offering a reason for their word choice in the course of the language game itself. One could replace one word for another without changing the meaning of a statement. For example, one could use letters to refer to particular slabs or use numbers as a substitute for letters. As long as the conversers understand to what the letters or numbers refer, the particular words are not that which produces the meaning of the statement. For Wittgenstein, in a large number of cases, the meaning of a word is determined by its use in a language (2009, p. 25). Because of this, I choose to attend to what the lab members' discussions reveal about the meaning of the activities in which they are engaged.

The language of neurobiology is different than that of STS, sociology, or philosophy. This requires interpretive labor to make accessible how the lab's workers design experiments, evaluate design, and train their students to fields outside of neurobiology. The justification behind my translations of the significance of these neurobiologists' discursive practices rests upon a core theoretical and methodological intervention in this project – namely, that of the possibility of "empathetic validity," outlined in the introductory chapter. As I describe there, this is related to but phenomenologically prior to "tutoring one's audience in the competence systems" in which a given set of members are acting (Lynch, 1997, p. 104). This intervention

[109] "That is called 'sepia'" (Wittgenstein, 2009, p. 18).
[110] Wittgenstein's own example (2009, p. 11).

seeks to resolve a tension in localist explorations of science which provide thick descriptions in terms of members' categories and show the situated nature of knowledge production. Additionally, I also seek to communicate the significance of those practices outside of their native context (e.g. Galison, 2008; Kuukkanen, 2011; Shapin, 1998).

My aim through this intervention is to communicate, with localist rigor, aspects of the system of competencies in which the neurobiologists work and reveal how the actions of the lab members within these systems speak to concerns in STS. This translational and communicative work, I argue, is also present in Lab X's own practices of designing and evaluating experiments through constituting their biological models as speaking subjects. I aim to set the groundwork to make the claim that a fundamental part of the lab's justificatory practices involves translating the biological phenomena they witness into communicative subjects to which they accede epistemic authority. These neurobiologists often step outside of providing descriptions of the behavioral and neural activities they observe and provide new and subjectifying categories to make sense of the phenomena they are studying or plan to study. More strikingly, they develop new categories as a part of remaking and upholding their standards for making objective claims about neural phenomena. These categories are not themselves "objective," i.e. the lab members do not use them as statements about how the biological phenomena *really* are. Instead, these categories are used as means of making the products of their models attain the lab's standards for objectivity.

In a similar way, the categories of analysis that I advance and develop here are not claims about the way things in the lab meetings *really* were. However, they are useful for communicating my experience of the significance of the lab's everyday modeling activities to practitioners outside of neurobiology. This motivation to communicate the significance of observations is a central driving force is biology. A feature of biological research is that the

"factiveness" of a claim is strengthened as other practitioners confirm the findings and rely on that claim to support or explain new findings. Intersubjective agreement is essential to the field and biologists go to great effort to communicate their findings in a way that is intelligible to their audiences. This often involves translating their observations into the media in which their broader field traffics, e.g. diagrams (Sheredos, 2017). Just as I have learned competence systems in neurobiology and now am translating the practices within those systems to a broader audience, the biologists also undertake a parallel process when translating their observations into forms and categories that are meaningful to members of their broader field.

The categories I believe best communicate the significance of the lab member's practices of designing and evaluating experiments and training students are those of: subjectification and ideal typification. While these concepts appear in several different domains of discourse, I intend to draw only from Gurwitsch's discussions of how others are constituted in terms of their roles in interactions, Schutz's early work on social interaction and ideal types, and Husserl's articulation of the constitution of "the person" – however I will call it a "subject."[111] Unlike Husserl, my analysis is not transcendental and, therefore, is not concerned with the essential features of a subject as such. Instead, I am concerned with subjects as they are constituted in conversation and how that activity is important to the conversers' epistemic achievements. However, Husserl's account of the essence of the constitution of the non-transcendental or personal ego is useful for

[111] This is an intentional departure from Husserl, who wants to reserve the word "subject" to refer to an animate organism that has sensations, reactions, a history, and some sort of psychical reality. A person is a distinct kind of ego formation that is constituted in relation to the world and other people and things. A person has judgments, perceptions, and motivations. A subject is required for the constitution of personhood, but it is not affected by personhood. This is distinction is important in Husserl's phenomenological project; however, because mine is focused on social interactions, I am necessarily looking at what he would call "persons." However, in contemporary phenomenologically inspired work, "person" is a loaded concept that refers specifically to humans in their situatedness. Because Husserl seems to regard persons as kinds of subjects that we recognize as something like us. This seems to be a matter of with what one can empathize. In the case of Lab X, they empathize with their mice and neurons. Because the word "subject" is used in contemporary phenomenologically or post-structurally inspired work, I use that word to refer to what Husserl would call a "person."

thinking about the unfolding of specific interactions that constitute biological material as subjects.

I use Husserl's articulations of how a person, or personalistic ego, is constituted to reveal how biological material stands in relation to the lab members as subjects in interaction. Husserl contends that in lived experience, one recognizes oneself as a person in relation to the "real circumstances" of the surrounding world, which "are exclusively the things or persons and their qualities and relations, etc., of which the subject is *conscious* as objective reality (for instance, what is actually experienced by the subject…" (Husserl, 1980, p. 339). One's own personhood is constituted as an intersubjective unity with other personalistic subjects and objects. Husserl claims in the shared world, others and oneself exercise and undergo "causality" and thereby "preserve their identical substance, the identity of the person" (1980, p. 339). Causality in this case refers to the features of realities that depend upon each other in the mode of change (Husserl, 1980, p. 133). For Husserl, a person is a unity that continues to be so in the face of change in the circumstances in which it finds itself. A person itself is constituted "only in a personal association… the word "person" designate[s] *a kind of being that is in principle relative* – similar to "material thing," which is what it is only within a possible thingly nexus" (Husserl, 1980, p. 332). What is significant here is that a person is only that in relation to others like it.

In the case of Lab X, I use Husserl's conception of this intersubjective constitution to describe how neurons come into being as subjects in certain kinds of interactions. In these interactions, the lab members accord to them judgments and perceptions which play significant roles in the activities of experimental design and assessment. These acts of judging and perceiving are ones that the lab members also perform, so there is a kinship grounded in this interaction. Once this shared activity ceases, the neurons are no longer like the lab members

because they are not recognized as being able to do the same kinds of things as the humans in the lab. For example, the neurons are not seen as being able to contribute to discussions about publication or budgets. However, in the context of the lab's epistemic work, the neurons are constituted as subjects whose judgments and reflective "statements" have ultimate authority.

I use Gurwitsch's discussions of roles in *Human Encounters in the Social World* to explore how members of Lab X constitute biological material explicitly as interlocutors for discussing disease phenomena. Gurwitsch contends that those engaged in a social interaction know each other through the roles in which they are performing. In articulating this, he provides the example of workers laying stones in a street. Both workers orient to each other through the common task of laying stones and relate to each other, therefore, as fellow workers (1979, p.104). For Gurwitsch the concreteness of shared tasks enables those involved in them to constitute each other as meaningful parts of the moment. The understanding of each other that they achieve in the shared task is determined in the unfolding of a situation in its concreteness and how they comport themselves in it (Gurwitsch, 1979, p. 107). Gurwitsch summarizes his approach to analyzing the meaningfulness of other subjects in interaction in the following excerpt,

> "The partners encounter each other in their partnership-situations in these roles constituted by the relationship to one another; they encounter each as the ones who are what they are in the particular common situations, e.g., as fellow workers as buyers and sellers, as employees and employers, as masters and servants, and, more particularly, in just the roles which they have in the concrete case – as the coachman who carries the passengers on a journey, etc." (1979, p. 108).

Significantly, Gurwitsch is concerned with interactions in which the partners constitute each other as individuals. This is different from how the neurobiologists constitute the neurons with which they interact. First, as far as I can tell, the neurons are not reciprocally constituting the biologists as interlocutors. However, these biologists are constituting the neurons as being

capable of answering specific questions and, more strongly, being in a conversation. Second, to make strong epistemic claims, Lab X does not rely on the results of one neuron. Instead, they determine a commonality across many dishes of neurons. Their results are an aggregate of the data they produce through that manipulation they performed upon many neurons. Yet, in their discussions, they refer to either neurons as a whole unit (e.g. "the old guys") or to a single neuron (e.g. "the presynaptic neuron says…").

The way in which the lab members discursively constitute collections of parts and processes as a singular subject or class of subjects can be viewed through Schutz's discussion of ideal types. For Schutz, members of the social world can relate to others as types. One posits the concrete, but not specific, existence of an other when one returns home and sees that they have received mail. They know that a postal worker delivered it, but they do not necessarily posit a specific person, but draw on the general class of person who delivers mail. They posit the existence of an instantiation from the class of subjects that can be picked out by the title "postal worker," or something similar. Schutz calls this orientation to another "They-orientation" (*Ihr-Einstellung*) (1967, p.183). In They-orientation, an other does not appear as a particular individual; instead, they remain somewhat anonymous. In this way, a "they" presents as "typical." They-orientation is not dependent upon the experience of a particular person who then serves as the ideal model for others like them. Instead, a "they" is constituted through one's prior experience of and with others. How others typically behave with further specifications of "kinds" of people and their behaviors and natures become a stock knowledge. When imagining an other of a particular type, one draws on this stock knowledge. As I will show in the lab's discussions, the biologists typify parts and processes from large populations of neurons. This type is a subject, or a class of similar subjects, and is anonymous, much like the unknown postal worker

who delivers one's mail (Schutz, 1967, p. 195). What is striking, however, is that the typified neuronal parts and processes are constituted as interlocutors. As I will explore, this perhaps relates to a goal of biology which is to produce results that make claims that must be generalizable to cases outside of the ones a particular lab has studied. It would follow that if Lab X wants to make knowledge claims about the phenomena beyond that which they witness in their organization, their practices would have to include methods of generalization, one of which could be the typification of their experimental material.

By using the conceptual tools of subjectification, the constitution of roles and types, I aim to reveal how in training novice scientists as professionals capable of designing and evaluating experiments, the members of Lab X reveal their standards for achieving objectivity in their epistemic work.

5.4 Humans

This section describes a journal club meeting in Lab X in which a graduate student, "Shui," presented published papers on the neurobiology of AD and DS. This meeting is described in full in Chapter 4 and is referred to as "The Tau Project." While I discussed it previously to analyze how the experiential and conceptual become intertwined in practice, I also explained the biological phenomena under discussion so I could discuss it later without interrupting my argument with clarifications of the biological subject matter in question. In this section, I will return to "The Tau Project" and provide more information regarding the scope of projects in Lab X and how graduate students are trained. By focusing on how the lab members give Shui guidance on the scope of her project, I will show how humans, as objects of research,

are discussed and constituted in Lab X. Specifically, I am going to show that while humans are ordinarily accorded the status of "subject," this is not the case in experimental practice. The fact that this lab's research is explicitly on *human* cognition in Down syndrome and Alzheimer's disease is striking. As I will highlight in this case, the senior members of the lab are not interested in even considering "human data." I will show through this case that the lab, in practice, "de-subjectifies" humans with DS and AD within the context of their research. However, I will show that the aim of these conversations is not to "de-subjectify" humans, but to impart norms of how to design a project and the value of particular sources of data. I will accomplish this through briefly summarizing what I have described before in the previous chapter and supplementing background information that will make visible the lab's professional orientation to humans as experimental objects.

The first journal club meeting in which Shui presented was in August 2016 and occurred prior to her settling on a dissertation topic. She had described to me her ambitious initial project proposal which she presented part way through the meeting. This project would show how a particular gene (Dyrk1A) was involved in the generation of Tau, a protein which becomes mutated to form the hallmark "neurofibrillary tangles" in AD and how all of this impacted behavior. Drawing on Delamont and Atkinson's insights, this project is too ambitious to be a guaranteed success (2001). Shui, like all graduate students in Lab X, were expected to not merely pick an important project for their field, but to pick one that they could accomplish successfully, i.e. produce intelligible and meaningful results, within a few years. This project, *prima facie*, involved a prohibitive number of parts and processes to be a dissertation topic.

Every member of Lab X had focused only on one or two parts at most in their dissertation and further limited the scope of their projects by only studying them within certain processes

under specific conditions. For example, the most senior member, Lawrence, had studied the structure of Nerve Growth Factor and the most junior, Josefina, was studying axon growth in DS. Ming studied how the outer envelope of chloroplasts develop and how a specific protein facilitates the outer envelope's development and maintenance. In Ming's case, he studied two parts (chloroplasts and a protein); however, he limited the scope of his research to a process which involved both of them. Pei, like Ming, picked a similarly complex topic but also limited the scope of his project. For his dissertation, Pei studied endosomal retrograde transport. While endosomes can transport many different kinds of proteins, Pei confined his work to only investigating a single signaling receptor within primary sensory neurons.[112] Shui's proposed project, on the other hand, involved five parts: Dyrk1A, 3R-tau, 4R-tau, neurofibrillary tangles, and behavior; and four processes: the overexpression of Dyrk1A, its impact on Tau ratios, the development of neurofibrillary tangles, and how these parts and processes interact to produce behavior indicative of AD.

In addition to wanting to focus on multiple parts and processes, Shui also sought to justify her topic by relying on data from multiple models derived from rats, mice, and humans. This added additional complexity and uncertainty regarding the success of her research. While the three papers she chose provided data on all the parts and processes she was interested in investigating, the fact that it came from three different models would have required Shui to confirm the findings from the rat and human models in the mice. Not only would doing so be a considerable amount of extra work for Shui, there was no guarantee, for instance, that the correlation between the increased amount of 3R-tau and the development of neurofibrillary

[112] As you may recall, Shui ended up choosing a similar topic for her own dissertation work.

tangles in rats would also occur in mice (Yin, et al., 2012). However, Lawrence did not see how the results from these different models had anything to do with longevity.

"But how does this connect to longevity? If you want to talk about longevity, the longevity of a neuron. If you want to know what a cell is thinking, doing, going through and you ask individual neurons what is being enhanced. What are these young guys feeling? What are these old guys feeling? You can take part of the LC [locus coeruleus] in mice, use fresh tissue and ask them… 80% of the neurons die, but 20% are fine forever – they don't care!"

"Well I have some of the human data later which supports Dyrk1A regulating Tau expression–" Shui said while picking up the third paper.

"Yeah, but what do humans really tell us?" Lawrence said, cutting Shui off, "You can make a case for anything causing anything in a human. The mice are *really* important and this lab (pointing to the first paper) isn't using them."

It was then that Shui fully outlined the connection she saw between the three papers. She wanted to use the first paper, involving rats, to establish that it was an imbalance of 3R and 4R-tau, where there is more 3R-tau, that causes neurofibrillary tangles in AD. She wanted to use the second paper, involving mice, to show that there is a behavioral change when there is an over expression of Dyrk1A. Crucially, the third paper, which used cells with human DNA, would serve as a bridge between the AD rat model and the DS mouse model. This is because the cells containing human DNA were being used to makes claims about both AD and DS cognition. However, Shui relied on the assumption that the processes described in the papers could occur within the same system.

However, as Lawrence asserted through his comment, human data is not well understood and is so complex that "anything can cause anything in a human." Additionally, neither rat nor

human models are as important as the data which could come from mouse models. After Shui explained her reasoning, with many interjections from Lawrence and Ming, Lawrence gently dismissed her argument by finally saying, "these are three different models." This effectively dismissed the epistemic viability of Shui's assumed textually compiled model in which all these processes could occur. As Lawrence says, this is an issue because the phenomena described in these papers come from three different material models, which precludes assuming that the same kind of gene and protein expression occurs in each system.

Curiously, despite the fact that the overarching aim for this lab is to isolate the mechanisms responsible for neuronal dysfunction in age-related disorders in humans, humans as objects of research are not valuable.[113] While the ethical constraints that preclude research on humans and their brains, one could hypothesize that if it were possible to use data from humans, it would be epistemically valuable. However, Lawrence's dismissal of humans as objects of research shows that even though they are the target of the lab's work, human data does not have the significance to justify a knowledge claim on its own. While it may seem that his dismissal of human data is incongruous with the lab's intention to study human cognition, he explains his reasoning by saying that "you can make a case for anything causing anything in a human."

In this instance, Lawrence could either be referring to the sparse data surrounding human neurons in DS and AD research, or he could be indicating that he thinks that human biology is too complex to enable researchers to determine neurobiological causal relationships. Whatever the case, the indeterminacy of human data makes humans as objects of research not valuable. However, it is worth investigating how humans are constituted in the lab's discursive practices to see how the target of their research is figured in relation to objectivity. One might normally think

[113] Summarized from Lab X's website.

that the ultimate way to determine whether a model is similar in desired ways to a target is to go investigate the target itself. Yet in this case, it appears that checking a portion of the target, i.e. human genetic material, does not determinately confirm the similarity of the model, i.e. mouse genetic material. Because of this, while the neurobiologists want to explain human genetic and neuronal material, these objects are not the standard against which to evaluate the models. In other words, humans as they figure in this research, are not standards that determine what counts as objective.

This is reflected in how the lab members speak and don't speak of humans as targets of research. In the cases I am presenting, the lab members use subjectifying language when referring to different kinds of experimental material. They frequently are said to "say," "talk," or "ask" and said to "care" and "feel" various emotions. The regularity of this kind of language usage and the ways biologists used this language to draw attention to the design of an experiment and as a means of encouraging junior scientists not to jump to a conclusion made it a notable feature of lab meetings. For example, after this meeting, I walked with Shui and Ming back to the main laboratory space. Ming was giving Shui additional advice on how to rework her proposed project,

"You have to ask them what they are really trying to tell you."

"Yes, but I think the human [model] really supports what I am trying to do."[114]

"But it doesn't say much here."

Discussing this language usage with the lab members after the fact resulted in interesting, but not clarifying conversations. For instance, I asked Unaza after one meeting why the lab

[114] I have clarified that Shui is not referring to a particular human, but is speaking of the human model used in the paper she presented in the meeting. While she may have expanded her statement differently, such as by saying the human "data," "paper," "work," etc. all I want to communicate is that she is still referring to the work in one of the papers she chose for that day.

framed experimental design in terms of asking neurons and their components "deep questions." After all, they were not actually talking to the neurons as they were working with them. Unaza replied that, "Well, you kind of are, but not really." I asked Alberto, a senior scientist a similar question, figuring that he would have better insight than an undergraduate member of the lab.

"In the last meeting, Lawrence said something about 'asking' neurons how they 'feel.' Do they actually feel?"

"It's something we say," Alberto replied.

I followed up with Ming a week later mentioning the conversation he had with Shui walking back from the meeting in which she presented her proposal.

"What did you mean, you have to 'ask' the neurons?"

"I said that? Oh."

These responses lead me to surmise that while this subjectifying language usage is meaningful within particular interactions involving design and guidance on how to adopt a certain professional attitude toward neurobiological work, this meaning did not persist beyond the interaction. In a Wittgensteinian light, one could say that training a graduate student how to approach experimental design is a distinct language game where the aim of the conversation makes the use of subjectifying language meaningful (2009, p. 7). Additionally, drawing on an applied use of Husserl's conception of the constitution of "persons," the neurons cease to be regarded subjects as when the circumstances change in ways that preclude the lab members from continuing to see the neurons as such.

However, it is apparent in this case that this was not just a casual utterance. Ming and Alberto use this language for specific purposes. One is to adopt the right sort of approach to assessing the design of an experiment. The other is to communicate their professional standards

to a novice scientists engaged in coming up with an appropriate project. Notably the lab members did not reflect on how their language use guided their instruction and the course of their assessment. This does not mean that the subjectifying language was not important. First, the lab members were engaged in two interrelated tasks. First, they were trying to assess Shui's proposed project. Second, they were trying to impress upon her the professional and disciplinary conventions of their field. Carrying it further and adopting a Foucauldian perspective, one could argue they were trying to turn her into a certain kind of subject. This is all to say that all the lab members were involved in a complex set of tasks which demanded all of their attention. As someone who was not involved in assessing Shui's project or attempting to train her, I was able to focus on how they were all going about these activities. From that vantage point, I saw how this subjectifying language organized their practice.

With that said, Lawrence uses this kind of language the most and his comments in this meeting highlight the epistemic priority he gives to mice as subjects over humans as subjects. Significantly, he uses language that attributed specifically to mouse neurons an interiority which he did not accord to human neurons. Neurons from the "LC in mice" could be asked how they are thinking and feeling and, presumably, they would be able to answer these questions. While Lawrence does not specify that the neurons would respond, because he says this within the context of challenging Shui's interpretation of the articles as being able to address issues of longevity, it follows that he is expressing that mouse LC neurons could respond. His rhetorical question of "but how does this connect to longevity?" immediately followed by "if you want to talk about longevity…" indicates that he understands that Shui wants to study neuronal longevity, but he does not believe her project proposal actually focuses on longevity. His following statements regarding the mouse LC neurons is positioned as an alternative means of

studying longevity. While presenting research on LC neurons as an alternative, he notably subjectifies them by referring to them as "guys" which ought to be asked how they are feeling through the act of experimentation. This is in contrast with how he speaks of humans which, according to Lawrence, do not really tell us anything.

Additionally, Lawrence refers to humans in general and not as individual subjects. In this way he is typifying them, as Schutz contends occurs as an ordinary part of being in the social world. However, in this context, Lawrence is constituting humans more as homogenous "cultural objects" as opposed to subjects (1967, p. 182). This is striking because of the diversity of both human AD and DS. For example, AD can be inherited or spontaneous. In neurobiology, the difference between these two varieties determines the target of the research, its scope, and the justificatory work practitioners need to do when selecting a particular organismic model. Additionally, while 95% of people with DS have an extra copy of HSA 21, 4% of cases of DS a full or partial extra copy of HSA 21attaches itself to another chromosome. In the remaining 1%, not all cells have an extra copy of HSA 21 (National Down Syndrome Society, 2018). This is in contrast with mouse neurons which Lawrence also refers to in general, as opposed to particular neurons, but with language that gives them, as a group, the capacity to think, feel, and communicate with researchers.

Lawrence is not the only lab member who speaks about humans and mice, and their neurons, in this way. Ming, when speaking with Shui after the lab meeting, refers to mouse neurons as "them" and directs her to ask them questions. When Shui reasserts her confidence in human data, Ming refers to "the human" model as an "it." While "them" can refer to both things and subjects, Ming directs Shui to ask "them" questions, connoting that the mouse neurons are

not strictly objects. When referring to the human model, “it” remains strictly an object without subject-like qualities.

In this case, there are two related discursive accomplishments which reveal the senior lab members’ standards for objectivity as well as what professional attitude they are exhibiting as they are training Shui to adopt. The first is that humans are constituted in generality and not as subjects. Furthermore, they are not constituted as something in which the lab members stand in relation to in a social interaction for the purpose of accomplishing a task. The second discursive accomplishment is that when designing an experiment, the lab members constitute mouse neurons as an anonymous class of subjects with which they can enter into conversation about their experiences of aging.

This returns us to the question of whether a phenomenology of scientific practice ought to treat this case as one in which the biological-material-as-subjects are metaphysically constituted or if they are only constituted as such within the experiences of the lab members. Even though the lab members believe they are working with “real” things, i.e. real mice and real neurons, these objects do not persist as subjects outside of collaborative experimental design and assessment. Their subjectivity is only “real” when engaged in particular epistemic activities; however, the objects’ performance as subjects guide subsequent experimental interventions. Furthermore, the lab members make the subjectivities of these objects relevant when providing explanations of possible future experiments or the results of past experiments from other labs. When accounting for the everyday scientific practices present in this case, neither realism nor constructivism fully conveys the epistemic work Lab X does. A phenomenology of scientific practice would, perhaps, be useful for describing how practitioners negotiate the tensions between these opposing commitments as a means of making reality intelligible.

5.5 Mice

Whereas the lab members do not subjectify or individuate humans in their work, they do discuss mice as individual subjects. By this I mean that the lab members distinguish one mouse from another and attribute to them features such as agency, minds, preferences, and personalities. Perhaps this is not surprising because mice are physically present as discreet organisms in the lab while humans, as objects of research, are not. The physical presence of mice in the neurobiologists' working environment makes these animals a part of the lab's work even when the lab members are involved in other activities such as inputting data or cleaning equipment and the mice are similarly occupied with their own activities such as running on a wheel or grooming. The mice are an essential part of the lab's day to day operation whereas humans as experimental organisms are not. In this section, I will describe instances in which the status of the mice as subjects and as individuals was relevant to the work in the lab.

The lab members who care for the mice would sometimes attribute to them preferences, habits, and personalities when they spoke of them without positioning these assertions as claims about the mice as models. Instead, the lab members spoke of the mice as mice. For example, when the lab received three GCDS mice as gifts from their collaborating lab, one of which was female, Monica, the person responsible for the mice, started referring to her as a diva. The "diva mouse" was apparently very choosy about which pellets she wanted to eat. Monica also thought it was cute how much the mouse groomed herself. When the mice had been delivered to the lab in early 2015, Monica and Hana, a Japanese postdoctoral student were chatting before a meeting.

"It's nice to have more of the mice. How are they?" Hana asked.

"Oh, they're just fine. They had a nice cross-country trip," Monica replied.

Hana laughed briefly, "The plane ride must have been new."

"The one female is a diva mouse. She probably liked it," Monica said.

"Diva?" Hana asked, not seeming familiar with the word.

"She's just so picky with her food and she grooms a lot," Monica said, miming rubbing the side of her nose with her palm while smiling.

There were also contexts in which the lab members made note of how individual mice were unique in the context of behavioral tests. In these moments, the lab members treated the behavioral idiosyncrasies of individual mice as potential guides for future genetic or neuronal tests. For instance, during February 2015, the lab was having their GCDS mice run through a Y maze to test memory. Three of the mice consistently underperformed the other eight mice. Instead of dismaying that there was this deviance, the lab members were excited. Ming and Pei were running the tests and debated over whether or not there was a genetic variance that could explain the underperformance. They speculated that perhaps these three mice could have a genetic variation they had not detected when they had carried out the initial genetic screening they performed when they received the mice. Because underperformance in a test designed to assess learning and memory in the context of AD and DS research is desirable in models of these conditions, it was possible that these three mice were better models than the other five. However, it was unclear why these three performed poorly. Ming and Pei also speculated that perhaps they had been in kept in the same environment away from the other mice before coming to Lab X. In their discussion, they never spoke of the three underperforming mice as being deficient. Instead, as Pei expressed, they wanted to know "what makes these three special?"

Ming and Pei did not follow up and try to determine if there was an underlying genetic mutation which could be responsible for the mice's performance. The routine screening that their partner lab had performed prior to sending Lab X the mice was taken to be the deciding factor and that, if these behavioral differences were present in GCDS mice they received in the future, they would look into environmental factors. Ming and Pei decided, instead, not to use the behavioral data from the three underperforming mice. They determined that these mice were not representative of how GCDS mice "actually behave."

How Monica, Ming, and Pei spoke of the mice illuminates how the status of the mice as individuals and subjects is or is not relevant to the modeling of AD and DS. Monica's comments reveal that she can view the mice as subjects without simultaneously seeing them as models. While a mouse grooming more than normal can be an important behavior to neurobiologists using a mouse model of autism or obsessive compulsive disorder, it is not typically a feature that researchers treat as relevant in models of DS or AD (Graybiel and Saka, 2002; Silverman et al., 2010). In fact, because it is associated with neuronal receptor mutations, this sort of behavior could put into question the genetic correctness of the GCDS mouse model if Monica viewed it as pathological. However, Monica giving the mouse an affectionate moniker indicates that she was not treating the mouse as a model in this instance. Instead, her comments seem to be attributing to the "diva mouse" a set of preferences and a personality. The mouse's personality, however, was never treated as something that ought to be investigated further or as impacting its capacity to serve as a representation.

In both instances, the lab members referred to the mice using individualizing language. Monica specifically referred to one mouse and Ming and Pei referred to three mice exhibiting similar behaviors. However, the context of the conversations the researchers had shaped the

significance of them speaking of the mice in their particularity. Monica and Hana were casually conversing before a meeting and the focus of the exchange was about the practical issue of receiving new, and highly anticipated, mice. They were not discussing how the mice could be used as models even though the mice were created for the purpose of them eventually serving as models. Monica and Hana constituted the "diva mouse" as a subject as well by suggesting it had experienced something novel while being transported by plane. Additionally, Monica explicitly brought the mouse's potential preferences and feelings into the conversation. In the context of their conversation, the idiosyncrasies of this particular mouse were noteworthy, perhaps because they were funny or charming. However, these idiosyncrasies were not brought up in relation to whether the mouse would serve as a good model behaviorally or otherwise.

This is in contrast with Ming and Pei who identified three mice who were underperforming in a behavioral test which they intended to serve as an assessment of learning and memory. The behavioral test was intended to quantify the mice's subjective processes of learning and then recalling where the reward was in the maze. In this way, their status as subjects was a valuable part of the test. However, their idiosyncratic behavior had been relevant to Ming and Pei identifying those three mice in particular. As opposed to treating all of the eight mice as sufficiently similar sources of behavioral data, Ming and Pei questioned whether the three underperforming mice were actually representative of GCDS mice. While they were genetically consistent with that line, the biologists determined that their performance in the Y maze precluded them from being used as behavioral models.

From this interaction, we can see that members of Lab X sometimes regard the particularities of mice as obstacles to using the mice as models. In this case, Ming and Pei wanted to determine how the GCDS mouse line performed in learning and memory tasks. These

are relevant behavioral features of mouse models of DS and AD. Because the three mice performed quite differently than the majority of the group of GCDS mice, and the prior data they had on other GCDS mice, Ming and Pei decided to exclude these mice from behavioral tests, even though they expressed excitement that these mice could potentially tell them something about epigenetic factors that impact cognition in DS. For the biologists, the mice's idiosyncratic behavior made them unique to be used as a stand in for a model of human conditions. By definition, a model must be able to serve as a representation of some other phenomenon. For this lab, a mouse that has idiosyncrasies which affect its aspects, which are intended to be representational, it cannot be a model. For example, while it is possible that mice of the same line can vary in coat color, unless those working with them intend to use them as models of a single mouse fur phenotype, multiple coat colors in a population of the line does not preclude them from serving as models of other phenomena. However, if a biologist wants to assess whether a line of mice could be used to model fear response in cases of depression and all the mice perform differently, the researcher would not have evidence to use them as a models.

In this case, I would like to isolate a specific discursive accomplishment that emerges. In the context of conducting and analyzing behavioral tests, the lab members constitute mice as subjects. As opposed to the mouse neurons described in 5.5, the GCDS mice that Ming and Pei discursively isolate from the rest of the population because they cannot readily be typified due to their divergent performances. While this aberrant behavior is potentially useful, it prevents Ming and Pei from using them as a GCDS model. Based on this case, I argue that Lab X values models that they can speak of, and use, as ideal typifications that are grounded in concrete particulars. Additionally, the kinds of subjects they constitute as having the authority to make claims about

reality are not unique or novel subjects. Instead, they are subjects that represent a broader class of potentially subjectified material.

5.6 Neurons

This section describes a subsequent lab meeting which focused on Shui attempting to settle on a dissertation topic. Chronologically, this meeting happened in October two months after the meeting in which Shui presented her first idea for her dissertation project. In this section, I show how the lab members use conversation to reconstruct the material activity required to produce published data by Wang et al. (2016). By reconstructing the experimentation, the lab members assess whether it met their standards for objectivity. The two ways in which they assess this is by focusing on the design of the experiment and the presentation of the findings. By engaging Shui in a discussion on these points, they more senior lab members model the professional attitude they expect her to take when designing and assessing experiments. Through the lab's discussion of Wang et al., I argue that its methods for maintaining their standards for objectivity, which can be expressed through the concepts of subjectification and typification, emerge in the course of helping Shui decide on her project.

In early October, Lab X had another "journal club" style meeting. In attendance were myself, the lab manager, Lisa, an advanced graduate student, Josefina, Shui, Lawrence, a project scientist Pei, and a postdoctoral student, Hana. Lisa, Hana, and I were the only ones who did not speak during the meeting. Josefina had told me that Shui had decided to not develop the project involving Tau that she had proposed in the August meeting and this lab meeting would hopefully result in Shui having chosen a project. Shui's approach this time presenting in the lab's journal

club was different. She only presented one paper and she sought to extend the data in this paper to make a claim that the papers' authors had not made. In the interim between the August and October meeting, Shui had not carried out the experiment that Lawrence proposed. Instead, she shifted fairly quickly to focusing on "signaling endosomes," which is a topic a number of the lab members work on. After a brief discussion a couple of weeks before that day's journal club meeting, Lawrence had encouraged her to find a gap in the work on signaling endosomes that she could fill in with her dissertation project. The paper she presented was on this topic and was published in *Nature Communications*, which was much more current than the previous papers she had presented. It was titled, "Flux of Signalling Endosomes Undergoing Axonal Retrograde Transport Is Encoded by Pre-Synaptic Activity and TrkB" (Wang, et al., 2016). Shui had also replicated the experiment prior to the lab meeting with the modification of using electrical, as opposed to chemical, stimuli. Before presenting a transcript of part of the journal club meeting, I will first provide a brief explanation of the various biological objects and processes referenced in this title.

This paper focuses on neurons and particular kinds of compartments within them, called endosomes. Endosomes are packages, bound cellular membranes, of molecules, ligands (molecules that bind to proteins), and receptors (proteins that bind with ligands) that were on the outside of the neuron's membrane. The authors of this paper focus on endosomes that move away from the axon and towards the cell body. This process is called retrograde axonal transport. During this journey back to the cell body, endosomes sort the material they acquired from the external side of the cell membrane. During endocytosis, the cell membrane bows inward, and the outside of the cell comes together to pinch together and release the newly formed endosome (See Figure 4.1). Wang et al. use fluorescent tags to make the molecules and receptors they are

investigating appear green and purple. They do this because they cannot highlight the outer membrane of the endosomes. To track endosomes and determine what molecules and receptors they are transporting, the practitioners have to make visible the endosomes' contents. It is standard interpretive practice to look for an overlap of receptors and ligands, which Wang et al. tagged with different colors, and determine whether or not the overlap means that there are endosomes present. To make clearer the parts and processes Wang et al. investigated in their paper, I have drawn a diagram (See Figure 4.1). This illustration depicts both endocytosis and the path the retrograde endosome takes.

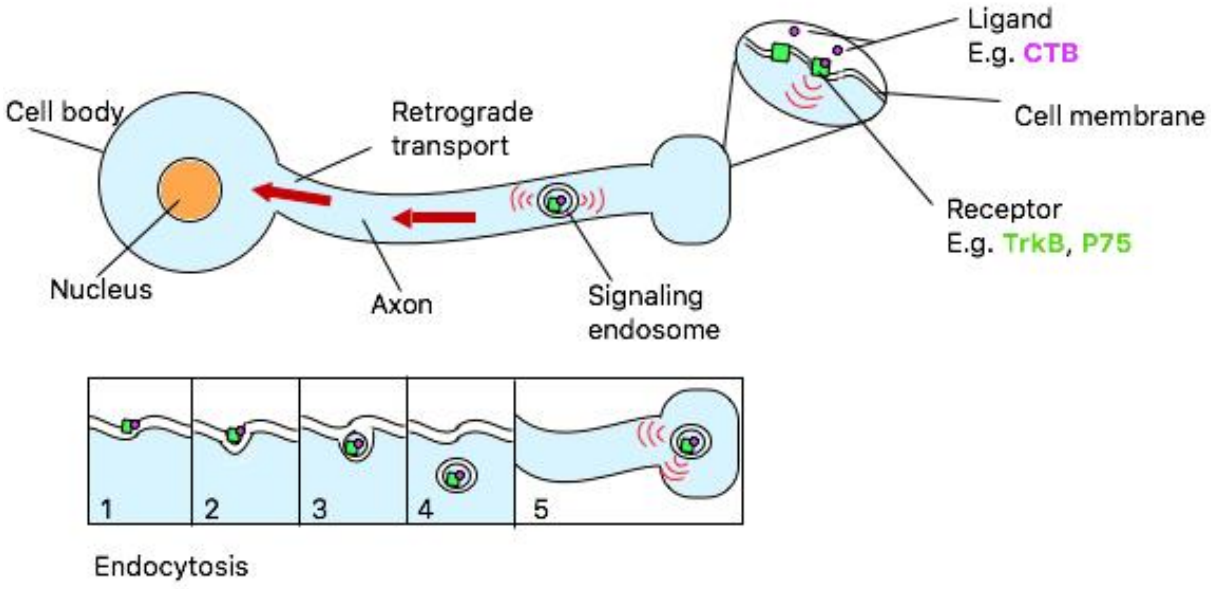

Figure 5.1 Axonal retrograde transport of a signaling endosome.

During the lab meeting the members worked together to determine whether the was an overlap. The significance of this was that the members questioned whether the experiments in the paper actually involved endosomes. Not only do Wang et al. claim that they are studying endosomes, they assert that they are investigating signaling endosomes. Extracellular signaling occurs in and between cells and helps cells coordinate their actions. Intracellular signaling occurs

within a cell and happens when different parts coordinate with each other through releasing chemicals which start and end processes and govern where resources are sent. Lab X has pioneered research on how endosomes can signal intracellularly, which means how endosomes release chemicals into the cell in order to affect intracellular activity. Wang et al. (2016) argue when TrkB receptors are in endosomes (which were originally embedded in the external membrane of the neuron) and are activated (i.e., have a molecule bound to them), they send out chemical signals to affect the cell's activity.

Wang et al. attempt to show that the specific activity activated TrkB receptors are involved in while in retrograde endosomes is that of promoting the health and survival of the neuron. The researchers also studied the receptor p75 because it also promotes the survival of neurons. Wang et al. do not claim that it is the signaling of these endosomes that promotes the well-being of the neurons. Instead, the authors focus more generally on the retrograde activity of endosomes containing these receptors as contributing to the well-being of the cell. The authors did not investigate whether it is the number of endosomes, what they are carrying, or their signaling, or some combination of these factors which contribute to the health of the neuron. Shui had attempted to replicate their results using electrical currents, instead of with Wang et al.'s technique of using large amounts of potassium to provoke endocytosis.

The topic of this paper has relevance to Lab X because not only are they interested in signaling endosomes, their focus on neurodegenerative diseases makes receptors involved in promoting the health of neurons a particularly apt target of study. A question that Lab X has had is whether a possible therapy for age-related neurodegeneration could be to deliver extra TrkB-specific ligands to neurons in order to prevent cell death. Wang et al. (2016) provide additional data on a way in which TrkB contributes to the survival of a neuron.

Shui began her presentation of the article by saying that she wanted to study how the signaling of these endosomes specifically contributes to the well-being of a neuron. She wanted to claim that the paper showed that not only were the P75 endosomes signaling, but so were the TrkB endosomes. She wanted to do so in order to claim that because these TrkB endosomes signal, the cell receives an impulse to engage in activities to promote its survival. However, the ensuing lab discussion called into question whether: 1) the paper said that TrkB receptors could actually signal when in an endosome; 2) any of the endosomes in Wang et al.'s paper were demonstrably signaling; 3) the way the paper, and Shui, had induced activity that was biologically plausible and meaningful.

In the course of the meeting, the lab members raised their concern that Wang et al. had not studied endosomes. Additionally, they questioned that even if the paper was reporting on endosomes, it was unclear whether they were *signaling* endosomes. These issues came up in the first half of the meeting, which I will analyze in Chapter 4. Below is an excerpt from the transcript of the latter half of the meeting, of which I made an audio recording. The transcript starts after Lawrence had communicated several times to Shui that he was unconvinced that Wang et al. had offered sufficient justification that what they were investigating were endosomes. The discussion took on a different objective at this point, which Lawrence articulates through his reflection on how he had thought about Shui's proposed project after he had read Wang et al.'s paper. Lisa and Josefina revealed to me after the meeting that Shui had described her new project proposal to Lawrence prior to assigning the paper for that day's meeting, so he

had it in mind when he had read Wang et al.

128 L: So I sat there thinking, "How can we rescue Shui's project?" And I thought of a couple
129 of things. First was, we need physiological meaningful stimuli. By the way, if you think
130 about the biology of this project... And I really like the paper. I think it is a great paper, it
131 is just misleading. What they are telling us that this guy here [the neuron] is only talking
132 to himself. They're saying that if I activate this guy [the neuron], I can activate the
133 receptors and get them to come back to the cell body, regardless of what goes on in the
134 target. That's nonsense.
135 S: Well, (unclear, possibly "I don't know about that")…
136 L: That's a tumor! That is a tumor cell! That is what tumors do, they talk to themselves.
137 They ignore their neighbor and talk to themselves! So there makes no sense in circuit
138 biology to have a neuron talk to itself and ignore its target. It makes absolutely no sense
139 whatsoever. And I can tell you with the biology of growth factors is the size of the target
140 is proportional to the trophic competency and that the amount, the concentration of
141 released Nerve Growth Factor is proportional to the trophic competency and that the
142 percent retrograde transport of the neurotrophic factor is proportional to the trophic
143 competency. [Ying Yue] has made this very clear. She's done this antrogradely for
144 BDNF and it is very clear. So, *this* [growth factor] says, "guys, just forget about the
145 target! It's meaningless. Just stimulate this neuron and everything is going to be fine." So
146 they don't prove that the endosomes can signal. This is the empty endosome theory. So
147 where's your project fit?

In the foregoing exchange, Lawrence asserts that Wang et al. do not use "physiologically meaningful stimuli" (line 129). This means that, according to Lawrence, the paper did cause endocytosis using a concentration of chemicals that would actually be present in a whole living system. Additionally, Wang et al. did not use neurons that were connected to other neurons. While this might not be a problem in other experiments, because the authors of the paper were flooding the area around the neuron with potassium as well as an assortment of receptors and ligands, this was not an investigation of strictly intracellular processes. In the target system of the human brain, this phenomenon Wang et al. were modeling would occur in a synapse, i.e. the space between the dendrites of one neuron and the axon terminal of another. Lawrence finds it nonsensical that a neuron would start producing endosomes in the absence of receiving a stimulus from a neighboring neuron (line 137). He then distinguishes previous work on a project scientists did in Lab X from that which was reported in Wang et al. Whereas Ying Yue demonstrated BDNF in endosomes undergoing retrograde transport does signal, because Wang et

al. have not demonstrated that the endosomes which they proport to be investigating have anything in them, they cannot be said to be signaling. This causes a problem for Shui because her project proposal rested on the assumption that Wang et al. had shown that the kinds of endosomes she wanted to look at were signaling.

148 L: The endosomes we are looking at require at least one molecule of the neurotrophin to
149 be here to keep that process going on. That's the argument. Why? Because there are
150 phosphatases out here that are incredibly active. And trying to kill the signal… You want
151 to basically to kill, constantly attack that TrkB activated receptor to keep it turned off
152 unless there was some active signal principle going on here. Right?
153 P: Couldn't there be- I've heard some tyrosine receptor it can- dimerization can induce
154 autophosphorylation.
155 L: It can. And if overexpress TrkA by two or three-fold-
156 J: Yeah
157 L: It isn't that the NGF has some special meaning. The only meaning it has is to dimerize
158 the receptor. But you either have to massively increase the concentration of the Trk
159 receptor to do this or you have to keep a little NGF around.
160 P: Or it can just induce a shift of-
161 L: If you could keep potassium. If you depolarize the cell and it could continually beat on
162 that endosome, only then it is a problem... We know in this experiment you had to get
163 TrkB to the surface to activate it.
164 P: Yeah.

In the preceding exchange between Pei and Lawrence, Pei responds to Lawrence's claim that the phosphatases will work to prevent signaling by keeping the TrkB receptor turned off (lines 148-152). In Lawrence's statement, there was an implication that something would be happening with the TrkB receptors where they would be inclined to signal, which would cause the phosphatases to work to inhibit a signal. Pei suggest that the receptor autophosphorylating would account for why the phosphatase enzymes would be working to keep the TrkB receptors in their original shapes (line 153-154). Lawrence notes that in Wang et al., there was an over expression of Trk receptors that would autophosphorylate. Without a similar increase in phosphatases, the majority of the receptors would be activated and sending a signal. Lawrence seems to anticipate Pei's suggestion on line 160 that a "shift" in neuron's charge would induce the production of synaptic vesicles, which are membrane lined packets that transport

neurotransmitters or receptors to the surface of the neuron. This depolarization could occur in response to increased levels of potassium and would have gotten the Trk receptors to the surface of the cell, which Wang et al. needed to do (line 163). This would enable the receptors to bind with the ligands that Wang et al. introduced around the cell.

166 L: I don't know why. Maybe it was the local concentration of it… The question is, would
167 potassium work on this system? And I think not. And here is the reason. There is a
168 fundamental piece of the biology and you've got to target. The only reason for you to
169 limit is to have a target. If you could keep yourself alive, you don't need a target.
170 P: I just guess maybe it isn't interested in clustering the TrkB receptors.
171 L: Sure!
172 P: It might want them to go inside-
173 L: Sure, sure, sure! So imagine you have TrkB sitting in a compartment here. I think it
174 even alluded to the GLUT1 transporter. GLUT1 is this guy that pops up when he senses
175 signals. It pops receptors up to the surface… So if activity may cause these receptors to
176 sit here and pop up to the surface and then occupy a domain in which they are clustered
177 together very tightly. And that would be very transient cause what you would expect it to
178 do is pull them back down in an endosome or two… So when you [to Shui] tell me you
179 get Trk activation for five minutes, I know it is not a signaling endosome. Because, by
180 definition, a signaling endosome signals all the way into the cell body. So [Josefina] what
181 do you think?
182 J: I agree! The p-TrkB signal doesn't die in other, um, plots I've seen from other people.
183 They show, 30 minutes later they are still-
184 L: Well we could isolate endosomes from siatic nerve or on it. Their kinase activity can
185 translate to an artificial substrate *in vitro* so they signal. So I think they've done a great
186 job. I think is a really cool paper. Because what it says is that activity is important for
187 this: for increasing the receptivity to the BDNF sitting out there, which then binds and
188 keeps the signaling endosome on.

In line 167, Lawrence reiterates the significance of remembering that the target of a neuron is important for understanding its activities. In line 168, Lawrence explains that neurons have limits on the amount of potassium they take in because too frequent firings of neurons, caused by depolarizations, can harm neighboring neurons. Furthermore, it is the connection between neurons that maintains their health, which enforces neurons limiting the frequency of their firings. In line 177, Lawrence hypothesizes that the number of receptors pushed to the surface would encourage the production of endosomes to clean the membrane of the neuron. This would pull the activated receptors back into the cell. However, he notes that because the Trk receptors were only active for five minutes in Wang et al.'s paper, they would not be signaling

endosomes because those return to the cell body instead of lingering near the edge of the axon terminal (line 178). Josefina confirms this by supplying that endocytosed phosphorylated Trk receptors signal for at least thirty minutes as they make their way to the cell body.

S: And the p-CREB tells you its signal can actually reach the cell body?
L: Where is the p-CREB signal?
S: After adding the-
L: Where is the p-CREB in the cell body? In this paper?
S: Um… in the middle?
L: In [Ying Yue]'s paper, yes. In [Zhu]'s paper, yes. I don't see it in this paper. *That* p-CREB (nodding at paper) is from the dish. They harvest the whole dish. They show you CTB in the cell bodies, they don't show you signals in the cell bodies. (pause) So it's a great paper in many ways.
S: Does the western plot count?
J: They didn't know.
P: No, no.
L: Not unless they harvest the whole culture, no.
P: (unclear) maybe in chambers-
L: It's five minutes.
P: Yeah.
L: It's all five minutes.
P: What if they did that in chambers?
L: If you did it in the cell *body* side of the chamber, *yeah*!
J: So p-CREB may have absolutely nothing to do with endocytosis.
L: Yeah. They didn't show you p-ERK or p-TYR, but anyway you can't- so think about it: they're stimulating for five minutes. They're harvesting for western plots… and they're waiting two hours to image.
J: That is a long time.
L: So, my comments were (pause) uh. This is the case of the empty vs. signaling endosome. This is the empty endosome. Well, I shouldn't say that. It is the *mute* vs. the signaling endosome. So I could be wrong, I could be totally be wrong, but this gives you then- and I really like the paper, but it says look: what the presynaptic neuron is saying, "I'm listening! Look, I'm *really* listening to my target. Are you out there? And I'm listening with my TrkB receptors, but I'm expecting you to give me some information. So I am going to keep listening as long as I am active as long as I am active. My listening is going on for ever and ever. And I'm an active axon. I'm going to be active and I'm going to keep putting my TrkB receptors out there. And soon as you have got some BDNF for me, I'm going to change. As soon as you get some p-TrkB back to me in the cell body, I am going change my genome and respond." And, by the way, [Josefina], it could be that this TrkB is enough to do some work in the axon terminal. It could be that the activated TrkB in the terminal is strong enough to signal through important modified proteins, protein synthesis, but this guy is *on*. He is revving *constantly*. I don't know, once per second or five times. He is *listening*. He's making TrkB come out here. So there's a conveyor belt of these endosomes coming in but they're not going to make a difference until they listen to the target.

Lawrence then concludes by offering his recommendation of how to proceed with a modified version of the project she had proposed.

230 L: So [Shui], that's the thing you should focus on, and you should use some of these tools
231 and have fun with that! Right? So the argument would be that activity alone will not
232 deliver a signal, or at the very least, a very weak signal. Whereas activity plus BDNF
233 does. And you'll probably have to go over the same territory, but not so much. And then
234 the question is, what is the physiological– (sigh) I really don't know. The worry that I
235 have is the *physiological* signal you are trying to deliver is still too crude. I mean, I'm not
236 disputing anything you are saying. I just want to make sure we're not just driving these
237 neurons crazy with too much current, you know what I am saying? So how do we do that
238 gently? And by the way, high potassium is a pretty big deal. I mean, that's like *whoa*!
239 That's like a tsunami hit the cell *pow*! It's like being punched, right? (laughs) (unclear)
240 But the idea that it is just *so* powerful. So the question is, what is the right thing to do? So
241 the paper, the work that you do would be more valuable in the context of, "Oh I see. I've
242 got a neuron that is being stimulated in a very gentle way. There's a certain amount of p-
243 TrkB already there. At least there was when there was low potassium. That's very very
244 nice. But that means nothing unless there is BDNF being handled in the axons, in terms
245 of signaling. So think about that. Let's think about a physiologically meaningful
246 stimulus…

In this meeting, the lab members subjectify and typify neurons and their receptors in the course of collaboratively assessing the design of Wang et al.'s experiment. Lawrence initially introduces "the neuron" as a guy in line 132 saying "They're saying that if I activate this guy, I can activate the receptors and get them to come back to the cell body, regardless of what goes on in the target." As he outlines his thoughts about the problems with the experimental design, it becomes clear that the neuron having subject-like qualities is important for determining how to correct the design. In line 136, Lawrence portrays an issue with the experiment as a guy talking to itself. This, he says, is what tumors do. He appears to see this as a problem because Wang et al. were trying to model neurons in humans using mouse neurons and were not trying to represent tumors. By comparing a neuron to tumor cells that talk to themselves and ignore their neighbors, Lawrence portrays the neuron as behaving pathologically. While this relates to his call for a physiologically meaningful stimulus (line 129), he describes the neuron using language in the way one might refer to a psychological disturbance. Because of his instance on neurons as

being affected by their connection to other neurons, the idea of one ignoring its neighboring neurons and not "talking" to them is a striking thought. The subjectifying constitution of a neuron as a guy that can talk and ignore highlights Lawrence's belief that Wang et al.'s design is flawed and also hints at a perspective one could adopt when reworking the experiment.

Lawrence continues on and gives a voice to the Nerve Growth Factor (NGF), which he locates as the cause of the neuron "talking to" itself. He reports the NGF saying, "'guys, just forget about the target! It's meaningless. Just stimulate this neuron and everything is going to be fine.' So they don't prove that the endosomes can signal" (line 144). The NGF, in this case, appears to be speaking to other NGF molecules. By constituting the NGF as speaking subjects, Lawrence emphasizes what he sees to be the biological implausibility of the experiment. He supports his conclusion that Wang et al. do not prove that their endosomes signal by attributing the capacity to reason to the NGF. Significantly, Lawrence reaches a final conclusion that Wang et al. are not reporting on signaling endosomes through giving voice to the NGF. This conclusion functions as final because Lawrence changes the objective of the conversation to determining where Shui's project would fit in the absence of the support on which she intended to draw for her project (line 147).

Lawrence is not the only lab member who uses subjectifying language. Pei similarly constitutes the neuron as having preferences and intentions. Specifically, Pei says that the neuron is, perhaps, not interested in clustering its TrkB receptors (line 169) and may, instead, want them inside the cell body (line 171). Pei attributes preferences to the neuron as a part of figuring out what happened in Wang et al.'s experiment. An unspoken question is, "if Wang et al. were not producing signaling endosomes, what were they producing when the activated receptors went into the cell, but remained close to the membrane?" Pei first expresses that perhaps the neuron

did not want clusters of TrkB receptors. Instead, it may have wanted to bring them into the axon terminal. By constituting the neuron as having made a choice based on its preferences for one thing to happen over another, Pei raises the possibility of another process occurring within the cell apart from the ones he and Lawrence had been discussing. Pei's attribution of independent and subjective desires to the neuron guided his, and Lawrence's, discursive inquiry to search for other reasons for why the neuron was recycling the receptors. Notably, neither Lawrence nor Pei attempted to find a way to justify Wang et al.'s explanation of the neuronal activity. Additionally, they did not posit what the fact of the matter was about the neuron. Instead, they discussed the experiment in a way that ceded authority to the neuron as a subject with its own reasons and desires.

Lawrence took up Pei's suggestion that the neuron may have its own preferences for not wanting TrkB receptors clustered on its membrane. He offers an alternative explanation for why this might be the case. "GLUT1 is this guy that pops up when he senses signal" (line 173). It pops up in areas where there are clusters of TrkB receptors because it is attracted to activity. After supplying the area with energy for autophosphorylation, the neuron registers the activity, and recycles the activated receptors by bringing them into the axon through endocytosis. Their activation would be temporary and they only would enter the neuron because of GLUT1's work to bring energy to those receptors. In this instance, the GLUT1 transporter protein is discursively constituted as a sensing subject. After Lawrence's suggestion of how GLUT1 could be responsible for the TrkB receptors being brought into the axon he concludes that both Wang et al. and Shui, in her replication of their experiment, did not produce signaling endosomes (line 177). If either had, the receptors would have been activated all the way into the cell body. As with Lawrence's (lines 131-137) and Pei's subjectification of neurons (lines 169-171), their

subjectification of the GLUT1 protein was immediately followed by them concluding that Wang et al. were mistaken in their interpretation of their data and in the design of their experiment. Despite Shui's attempts to argue that the endosome returns to the cell body and signals (lines 188 and 192), Lawrence, Pei, and Josefina remain committed to Lawrence's conclusion regarding the role of the GLUT1 protein (lines 193-211).

Lawrence concludes the meeting with his overall assessment of Wang et al.'s paper during which he constitutes "the neuron" as a speaking subject. In highlighting what he does like about the paper he says that the neuron is saying, "I'm listening! Look, I'm *really* listening to my target. Are you out there? And I'm listening with my TrkB receptors, but I'm expecting you to give me some information" (line 216). Not only is the neuron speaking, it is speaking to another neuron. It hears with its TrkB receptors and has the expectation that another neuron will communicate with it. By saying this, Lawrence is expressing that Wang et al. demonstrates that the activity of the TrkB receptors is important for producing endosomes (line 227). Additionally, by characterizing the neuron is wondering if another neuron is out there, he is returning the conversation's focus to recognizing that the interconnectedness of neurons is essential to understanding what they do and how to design an experiment.

As he continues explaining his reaction to the paper, he subjectifies the axon specifically. "And I'm an active axon. I'm going to be active and I'm going to keep putting my TrkB receptors out there. And soon as you have got some BDNF for me, I'm going to change" (line 219). This shift to speaking as the axon specifies the part of the neuron that was relevant for Wang et al.'s experiment and what Lawrence eventually argues ought to be the focus of Shui's project (line 229). This is the portion of the neuron to specifically interrogate or, as was a frequent expression in the lab, the part to "ask deep questions." Lawrence's overall guidance to

Shui picks up on conversational moments in which the lab members subjectified neurons and receptors. Lawrence encourages Shui to use physiologically meaningful stimuli which he initially introduced when comparing the neurons in Wang et al.'s case to tumor cells. He also emphasizes the importance of the TrkB receptors which he and Pei discussed while constituting both the receptors and the neuron as a speaking subject. Additionally, the axon, which he subjectified earlier, returns as the site of the project which Lawrence recommends Shui undertake.

The lab members made significant steps forward in their assessment of Wang et al.'s paper immediately following each time they subjectified the biological material under discussion. In three instances the lab members' discursive work of constituting the biological material as subjects preceded them concluding that there was a flaw in the design of the experiment. In two instances, the lab members used subjectifying language while they were collaboratively determining what Wang et al. had been observing and a strategy for improving upon their design.

This portion of the lab meeting reveals that subjectification plays a role in how the lab members assess the objectivity of an experiment. In the moments in which they deployed this discursive method, they were able to reach a new insight on the biological phenomena described in the paper. Additionally, these moments of subjectification served as the final and unquestioned justification of the members' assessment that Wang et al. had not shown what either Shui thought they did or what they themselves had claimed. This highlights the important epistemic work of subjectification in Lab X's practices. An additional epistemic function of this discursive practice is that the lab members transfer authority about the biological phenomena to the parts that they constitute as subjects. In this conversation, the neuron had preferences for the

organization of the TrkB receptors. It also wanted to hear something from a neighboring neuron. These motivations, as they were produced in the meeting, became processes to investigate through further experimentation. The lab members did not offer explanations for why the neuron had particular motivations, but raised these preferences in a way that ensured that their own personal hypotheses did not predispose the lab to reaching an unjustifiable conclusion.

Throughout this analysis, I have followed the lab members language and spoke of "the neuron" as a singular entity. The lab members less consistently referred to "the receptor" or "GLUT1" as individual objects as well. Briefly considering the practical physical work that went into Wang et al.'s experiment and Shui's replication, none of these biologists based their data on a single neuron or single receptors or proteins. Wang et al. does not provide information regarding how many neurons they studied. Instead, they refer to plating multiple mouse hippocampal neurons in multiple dishes, but it is possible to arrive at a ballpark number of the number of neurons with which they were working (Wang et al., 2016, p.12). Mouse hippocampi are composed of, subject to variation among mouse lines, upwards of 5 million neurons (Insausti et al., 1998). If they were plating the neurons at low density, i.e. under 100,000 per dish, Wang et al. would have prepared over 1 million neurons in the course of their experiment. This is all to say that neither Wang et al. nor Shui were acquiring their data from anywhere close to only one neuron. Yet, the members of Lab X referred to these many neurons as "the neuron." This reveals that the singular subjects they speak of as having preferences and reasons are an abstraction from the relevant processes that occurred in the thousands of individual neurons used in the study. The processes the lab members discuss, presumably, occurred in the same way in all of the neurons studied. It would follow that because the lab members regarded the phenomena as sufficiently similar across all neurons that they could regard them as a type.

The lab members did not draw as much emphasis to typifying neurons and receptors as they do to their subjectifications of these objects. Nonetheless, their constitution of these objects as types that were potential interlocutors had significance to the lab's standards for how to design experiments in a way that affords the possibility of meeting their standards for objectivity. In this portion of the lab meeting, Lawrence returns several times to the need for a redesign of Wang et al.'s experiment to involve "physiologically meaningful" stimulus. This stimulus, according to Lawrence and Pei, would need to take into account that neurons are in communication with each other and modulate their activities based on this interaction. By giving speech to *the* neuron to have it say that it is listening to its target and asking if it is out there, Lawrence both draws attention to the focus of the project Shui could undertake as well as the attitude one should adopt in approaching this experiment. Specifically, Lawrence sees TrkB's capacity to signal and its role in coordinating with neighboring neurons as being worthy of investigating. Additionally, by constituting the neuron as an interlocutor that is aware of its commitment to "keep listening," Lawrence is positioning the neuron as something that can answer Shui through her experimental work. Importantly, the question Lawrence wants Shui to consider is "what is the right thing to do" (line 239).

The word "right" in this question has an ethical connotation. It appears in the context of Lawrence framing for Shui how he wants her to think about her project. He brackets the issue of choosing the "right" thing to do with his reluctance to drive the neurons "crazy" with too much current or "punch[ing]" them with too much potassium and his insistence that they treat the them gently. By portraying high levels of stimulus as violence and urging Shui to think about the right course of action, Lawrence is implicitly constituting the neuron as a subject worthy of ethical

treatment. This illuminates the attitude Lab X wants its junior members to adopt as neurobiologists, part of which is achieved by constituting biological material as subjects.

5.7 Insights on Objectivity in Lab X

This discussion investigated Lab X's practices of training graduate students to design and assess experiments. My analysis focused on what mattered to the lab members when it came to teaching the lab's junior members to develop their own projects in relation to gaps or issues in their field. By following Shui's process of proposing projects and refining her interests, I came to understand that a core concern of Lab X is doing work which meets their standards for objectivity. Their conversations across the three instances I presented here reveals that constituting biological material as subjects capable of entering into conversations is a method by which the lab members arrive at results that they see as generalizable, justified, and not from their own perspectives. This final section articulates how the cases I have analyzed above respond to discussions in STS and illuminate features of Lab X's knowledge producing practices.

The way in which subjectivity figures in the lab's practices resonates with the phenomenologically inspire literature in STS. For example, Maynard and Schaeffer see subjectivity as being relevant in "pre-hypothetical forms of knowing" (2000, p. 335). In the contexts in which Lab X used subjectifying language, they were not proposing formal hypotheses; instead, they were determining new courses of study which could lead to justifiable hypotheses. Additionally, the lab members' determination of whether Shui's pitches for what she would do for her dissertation involved collaborative deliberation of whether the inferences she wanted to make were justifiable. No one opinion served as definitive. Instead, the lab members

sought input from each other and modified their stances until they came to an intersubjective agreement on whether Shui's design was lacking. Rorty's claim that "objectivity is intersubjectivity" is an apt means for describing one of the standards Lab X has to meet for providing an objective claim (1987, p. 41-42). Even in pre-hypothetical forms of knowing, the lab members must be in agreement about their claims about the world.

Some accounts of objectivity in science characterize scientists as carrying out "the god trick" in which they deny their own role in the production of a fact (Haraway, 1988, p. 575). However, this is not Lab X's practices prior to their efforts to turn their results into a publishable paper. Additionally, the lab members appear to go out of their way to constitute the biological material they work with as "knowing and moral subjects" that have authority on the conditions which the lab investigates. One can see this in Lawrence and Ming's urging for Shui to inquire into how neurons are "feeling" and to "ask" models questions to get them to reveal "what they are really trying to tell you." Additionally, even in cases where the lab members were intentionally not using their mice as models. For example, when Ming and Pei decided against including three under-performing GCDS mice in their study, they still regarded them as having the potential to tell them something about epigenetic factors impacting cognition in DS. They still constituted these mice as knowing subjects. When collaboratively evaluating Wang et al.'s paper, the lab members spoke less of the biological objects as knowing subjects; instead, Lawrence constituted the neurons as moral subjects. By connecting the need to have a biologically plausible stimulus with the morality of not "driving them crazy," Lawrence impressed upon Shui the ethical value of using interventions that represent phenomena in the world.

Through examining the lab's training practices, I gained insight into how informal interactions served as means of professionalizing graduate students. While the lab discussions I focused on were informal in the sense they were part of the lab's ordinary business, they gave students the opportunity to do what fully trained scientists do (Campbell, 2002, p. 906). The lab members expected Shui to present another lab's paper, evaluate it, and apply it to her own work. While they frequently corrected her interpretation of the paper and steered her to identify problems with it, they maintained their standard for what they expect graduate students to accomplish. That is to say, they continued to expect her to develop a dissertation project which was executable and significant for their field. Furthermore, they did not relax their standards for how to evaluate the biological plausibility and justification of an experiment. Even though the case in 5.6 was Shui's second attempt at proposing a project and there was mounting pressure of her to pick a project, her lab members still enforced their standards for objectivity.

The two interrelated methods the lab members use to ensure their claims are objective can be productively characterized as subjectification and the constitution of particulars as a type, or kind, that can serve as an interlocutor. From the cases I presented, there are two epistemic functions that constituting the biological material as subjects serves. First, by constituting the material as having preferences, motivations, and reasons that are worthy of understanding, the lab members often looked for alternative accounts of what could be causing a particular phenomenon. On multiple occasions, this led to them redesigning an experiment or concluding that a hypothesis or claim was unjustified. Second, by constituting the material as speaking and moral subjects, the lab members granted epistemic authority to their models. As opposed to them trying to arrive at a view from nowhere as a means of obtaining objectivity, they sought to uncover and articulate the perspective of their models. The models, then, were given the

authority to answer questions and proclaim the fact of the matter on the disease phenomena they played a role in producing.

Constituting the material as types enables the lab members to both specify what is representationally relevant to a target phenomenon in the world. It also enables the biologists to make generalizable claims about objects outside of the lab. By constituting their material already as non-particular subjects, they have an understanding of a phenomenon that is not attached to any one particular material instantiation. Instead, they are discursively working with a subject that has been stripped of individualizing details. This is essential for a successful claim in biology, where success is determined by other practitioners in a field also being able to replicate and agree upon it.

The role subjectification plays in the lab's epistemic practices also breaks down the dichotomy between realism and constructivism in the philosophy of science when viewed from a phenomenological approach. In 5.6, Lawrence brings together "real" objects and the statements of a subjectified axon (line 219). Professional biologists agree that TrkB and BDNF are real objects that can be reproduced across experiments. The subjectivity of the axon, which says that it is an "active axon," is not a feature of biological research that other labs report on in publication. However, in this instance in Lab X, this subjectification is used to explain intracellular behavior and guide subsequent research. Lawrence even interrupts himself to say how this could explain and guide Josefina's research, "And, by the way, [Josefina], it could be that this TrkB is enough to do some work in the axon terminal" (line 222). In this moment, the lab orients around the constituted subjectivity *and* objectivity of an axon, the latter which they believe to be persistently in the world.

Throughout this meeting, the lab members discuss the subjectified biological material and the "real" biological objects to assess the paper Shui is presenting. This happens quite significantly when they discuss the cellular model as actually a model of a tumor as well as when they offer an explanation for why TrkB clusters. In each of these cases the lab members were able to assess the objectivity of an aspect of Wang et al.'s paper through this integration of subjectification and reference to, what they believe to be, mind-independent objects. Neither a strictly realist nor constructivist approach adequately account for how the lab members are able to accomplish this work. One could write off the lab members constituting biological material as subjects as merely a heuristic technique. However, this would not capture the lab members' multiple objectives in these discussions. First, they are trying to assess an experiment. Second, and quite importantly, they are also trying to turn novices, such as Shui, into professional who approach experiments in particular ways. For this lab, experimentation is, ultimately, about communication amongst each other, to biologists outside of the lab, and with the biological material itself. In these contexts, constituting a neuron as a subject is not a mere heuristic, but is a part of what it is to be a biologist in Lab X and a member of their broader field.

By viewing the lab's practices of meeting their standards for objectivity through subjectification has several consequences. First, it offers a new account of a scientific objectivity, which could be expressed as the answers biological material provides when asked an informed question. These answers are not statements without perspective. Instead, they are the thoughts, feelings, and reasons of a biological object pertaining to its own nature. Second, because the practitioners transfer the authority to make claims about the world to their biological models, the burden the biologists must contend with shifts from making objective claims, to making justifiable inferences and interventions. This shifts the conversation from being about scientific

objectivity or “Truth” to biologists’ practices of justification. Or, if one takes a phenomenological view, the conversation becomes about how practitioners arrive at intersubjective agreement and thereby determine the reality of aspects of the world. These practices can be understood without requiring a strong commitment to their being truths about the world independent of perspective. Instead, one can analyze a lab’s practices of justifying their interventions and inferences to each other and to their communities with attention to the rigor of the methods and their ability to elicit answers from their objects of study.

Chapter 6

Conclusion

I am going to conclude this project by returning to the questions which made me undertake this endeavor. These questions were: 1) What happened to the emphasis on public outreach that motivated the large-scale biology education outreach initiatives of the 1960s and 1970s? 2) How do contemporary biologists use communication (specifically pedagogy and communication with their field) as a means of producing their epistemic accomplishments – particularly their standards? I will then offer two ways in which STS scholars can productively intervene in the context of science communication. By doing so, I aim to answer a question which guided this overall project: what can it mean to do a laboratory study now during a time in which there are concerns that the epistemic authority of science is in jeopardy and how can one productively intervene in this climate? The two sites and methods of intervention I will articulate relate to the interfaces between scientific experts and the lay public and science education. These are not the only ways in which someone could intervene, but they are ones that have emerged for me in the course of doing this particular project.

I will first discuss what happened to the emphasis on outreach and education that motivated public outreach efforts such as those that the Council for Biology in Human Affairs. Chapter 2 began by describing how Jonas Salk's desire to improve public welfare motivated his research on poliomyelitis. For him, part of improving public welfare involved communicating the significance of his research to the lay public despite the resentment this provoked from the scientific community. The chapter then describes how Salk attracted other academics who also

believed that an informed public was essential for the proper functioning of biology. These men were the first Fellows of the institute and shared Salk's sentiments because of their experiences in WWII. Jacob Bronowski articulated this most poignantly when he described how his commitment to communicating the ethical significance of science emerged when he witnessed the rubble of Nagasaki. The chapter continues by describing the attempts the Council made to transform biology into a discipline that could address issues pertaining to society, ethics, and human nature. Bronowski intended for the Council to create lasting mechanisms that would make biological research intelligible to the lay public. He also wanted these mechanisms to give the lay public the power to set the field's research agendas and determine what would be done with the products of science.

The Council was not able to accomplish these goals. I would argue that this is because its members did not have the time to do this difficult work on top of their traditional lab work. Furthermore, they did not have the training or understanding of how to communicate the significance of their work to the lay public. However, their efforts still had effects on subsequent developments within biology. Members of the Salk Institute and their peers who were sympathetic to their humanistic motivations organized the Asilomar conference in 1975. This conference addressed ethical concerns regarding recombinant DNA research. Following the conference, its conveners organized public hearings that allowed the lay public to participate in developing NIH guidelines for DNA research. Members of the Salk Institute and conveners of the Asilomar conference were integral to starting and leading the Human Genome Project. One of the core aims of the Human Genome Project was to gain an understanding of the human genome. In doing so, biologists hoped to uncover information and create tools that would lead to cures for diseases.

The technological developments, particularly those involving model organisms, created communicative challenges in biology with regard to public outreach as well as within the field. Throughout the 1990s biologists developed smaller research communities around particular model organisms. Even if two labs were studying the same disease, they would still encounter communicative obstacles if they were working with two different organisms. They would have to translate the significance of findings arrived at in one organism to another, which required knowledge of both organisms. Starting in the late 1990s and early 2000s, disease-focused biologists began to work with particular genetically modified "lines" of organisms. This created an additional communicative challenge because researchers would need to translate their findings across model lines if they hoped to unify the research within their subfield. If members of an area such as Down syndrome research want to present accurate information to the lay public, they first need to integrate research across model lines and model organisms. Only then can they figure out how to present this to the lay public in a way that is intelligible.

As Chapter 3 shows, it is difficult to unify a subfield's research. Practitioners need to balance their standards for making adequate models with the practical demands of everyday work. However, making inferences across model lines and model organisms is essential for disease-focused biologists. This is because the accomplishments of biology are increasingly the result of teams whose members have expertise in particular model organisms and model lines. These teams are multi-sited and are comprised of practitioners in different labs, universities, and countries. The funding biology has enjoyed since the end of the Cold War has enabled practitioners to specialize, understanding relatively few areas in great depth. This has created a greater need for biologists to be able to communicate the significance of their work to other biologists who have different areas of expertise.

Chapter 3 shows that the emphasis on outreach is still present within disease-focused biology. However instead of biologists spending their time attempting to educate the lay public, they are focusing on communicating with members in their subfield, but who are outside of their areas of expertise. Chapters 4 and 5 show that not only are contemporary biologists concerned with communicating with those outside of their labs, but they are also devoted to training the next generation of biologists.

I will now address my second question which concerns how contemporary biologists use education and limited outreach as means of producing their epistemic accomplishments. My particular focus has been on how the members of Lab X establish and meet their standards. I contend that setting and meeting standards count as epistemic accomplishments in biological practice. The main way Lab X makes intelligible their standards for scientific work is in the context of training their junior members. This training is a very specific kind of communication which not only plays a role in professionalizing junior lab members, but also is a key part of the lab's epistemic work. In Chapters 4 and 5, I show how training students plays a large role in the epistemic accomplishments of the lab.

Chapter 4 describes two cases in which the more senior lab members are training junior members to turn mice into models of Down syndrome. In the first case, the lab director communicates to an undergraduate that knowing how to perform a procedure is more than just merely memorizing a set of instructions. The standard for knowing how to turn a mouse into a model is that one must appreciate the epistemic significance of the material activity. Furthermore, one is expected to recognize and value how the material activity of turning a mouse into a model fits into the community of practice (which is the lab). In the second case, a graduate student presents a proposal for her dissertation work. In this proposal she has discursively

created a model based on published findings from three different organisms. Through this meeting, the lab members communicate to her their standard for an adequate model. By communicating this standard to her, she changes her project. The lab members training the graduate student directly shapes the research that comes out of their lab.

Chapter 5 also takes a case of pedagogical instruction as the locus for the phenomena it analyzes. In contrast with the previous chapter, this one looks at how acts of communication are foundational for particular epistemic accomplishments. Here, I examine how lab members discursively constitute mice and their neurons as subjects. These subjects are able to state what the fact of the matter is about the conditions they are representing. In this lab meeting, the graduate student from Chapter 4 is presenting an alternative dissertation project. Through the lab's discussion of her proposal, their standard for attaining objectivity becomes intelligible. As part of ensuring the objectivity of their results, the lab members design and assess experimentation as though they are in conversation with a neuron. By doing so, the lab members determine the biological plausibility of an experiment or model and develop hypotheses. In this way, communication is central to Lab X's epistemic achievements.

I want to end by offering some tentative answers to my last question: what can it mean to do a laboratory study now during a time in which there are concerns that the epistemic authority of science is in jeopardy and how can one productively intervene in this climate? These are my current thoughts on the matter and my ideas for future work. The November 2016 elections provided a rather abrupt opportunity to reflect on how one approaches sites of knowledge production. In doing this reflection, I returned to the method and genre of laboratory studies while examining my approach to studying Lab X. This dissertation was an attempt to explore what it would look like to study scientists' matters of concern as they are revealed through their

everyday practice. In doing so, my project became more interdisciplinary. Because my scientists were concerned with things such as normativity, justification, and objectivity, my project explicitly engaged with areas in the philosophy of science that STS normally does not. Furthermore, because I was looking at everyday conversations that involved subjectifying language, I drew on older traditions within phenomenology, which the philosophy of science avoids. To make sense of the communicative practices associated with training in my site and outreach activities directed toward members of its field, I conducted historical research that focused on letters, grant proposals, and meeting notes. I contend that all these resources were necessary to adequately study Lab X's matters of concerns. By providing an account of their matters of concern I, therefore, have been able to show how these biologists are able to produce matters of fact and the difficulty of this task.

I came away from the historical and ethnographic research I conducted recognizing that making biological findings intelligible to the lay public is an unreasonable demand to put on biologists alone. However, I see STS scholars as being uniquely capable of increasing public understandings of science especially in the context of two particular sites.

The first site to which I could see STS scholars making a positive contribution would be at interfaces of expert and non-expert understandings of science. One option would be for STS scholars to play a role similar to a science journalist. However, they would be in a unique position to communicate the meaning and significance of science and health news to the public. Unlike a journalist, a traditional STS scholar employed at a university does not rely on selling their writing to make a living. Specifically, their jobs are not dependent on how many copies of their book gets sold.[115] Because of this, STS scholars who were inclined to translate their

[115] It is at least partially dependent on what their peers think of it and perhaps how many people site it, but their livelihood is not tied to the sheer volume of books sold.

ethnographies, studies, histories, etc. of science for a lay audience would not need to consider sensationalizing them.[116]

Another way in which STS scholars could work at the interface between scientists and the lay public would be in the face-to-face interactions between members of these groups. One site in which these kinds of face-to-face interactions occur is in the medical field between doctors and patients. While there are probably similarly structured interactions outside of medicine, based on the topic of my research, this one most readily jumps out at me. A doctor and a patient come together with different kinds of knowledge. A doctor is trained to diagnose and treat conditions based on patient histories, verbal reports, and empirical tests. A patient will most likely not have the same skills as their doctor but has the lived experience of having a particular set of symptoms, in the case of disease. This counts as a form of knowledge. In about 13-16 minutes, a general practitioner and their patient are expected to work together to determine an explanation for the patient's symptoms, what the disease is, how it could have happened, and how to treat it (Peckham, 2016). STS scholars could improve interactions between doctors and patients in multiple ways. Based on their likely training or occupation as an educator, they could improve the pedagogical aspects of the doctor-patient interaction. For example, STS scholars could demonstrate the value of soliciting questions or asking patients to summarize information a doctor has provided.

The second site I could see STS scholars productively improving public or novice understandings science would be in science education. STS scholars have a special competency in studying the sociality involved in science. They are especially well-versed in seeing how particular activities, institutions, and structures facilitate or preclude people from being able to

[116] This would require re-thinking tenure requirements and the value of public intellectualism.

become a member in knowledge producing communities. Many laboratory studies and STS texts with ethnographic components have shown how power relations are enforced through scientific work. A consequence of this is that people occupying disempowered social categories are excluded or erased from knowledge producing activities. A very visible place in which this happens is in the classroom. In the case of race in the US, despite an increase in the number of self-identifying black and latinx students, these students are less likely to pursue a STEM major and more likely to do worse in it than their white peers (Museus et al., 2011). Additionally, self-identifying women and latinx STEM majors are less likely to see themselves as future scientists than their white and men peers (Hazari, Sadler, & Sonnert, 2013).

STS scholars have the methodological and theoretical training to study how particular classroom dynamics and course design enforce the disempowerment of these groups. More significantly, I would argue that they are also positioned to improve classroom environments to make them more accessible to students traditionally precluded from seeing themselves as scientists or even as "science people." STS practitioners who have experience in laboratories as ethnographers or have collaborated with scientists have a unique skillset. They are able to understand scientific content from a scientist's perspective while also being aware of how an outsider would understand it because they know what it is like to be an outsider. With minimal training, STS scholars could collaborate with science instructors to create or redesign courses that create the necessary scaffolds that make science accessible to more students.

These sites of intervention offer additional opportunities to STS scholars who do community engagement as part of their research program. These sites would also make further use of the skillsets practitioners acquire when conducting ethnographies or pursuing collaborations with scientists. By extending these skills to improve public understandings of

science and science communication, STS scholars would also take up a latent objective that was present in Latour's ethnographic study. Specifically, laboratory studies could be used in a way that would fulfill the Council for Biology in Human Affair's goal to communicate the content and significance of scientific research for the purpose of empowering the lay public.

Appendix

This is the full transcript of the lab meeting presented in Chapter 4.

Shui (S): Today I want to review a paper that was published recently that is related to my project which is trying to understand whether the neuronal activity can increase the flux of signaling endosomes. In one word 'it can increase.' Um first, I want to introduce a toxin. It's called Cholera toxin and that's their reagents that the whole paper is using to probe the signaling endosomes. So CTB stands for Cholera Toxin sub-unit B.
S: So first, I will show you a diagram of how this toxin is normally degraded for example in small intestine cells. But that's not the most important part. I just want you to have an overall idea. It first binds to the lipid bracket and the goes to the endosome, golgi, and ER… So, this paper, they use this [CTB] as a method– a *labeling* method to label their retrograde transport. According to them they said "CTB converges with the neurotrophic receptor p75 at the level of early endosomes and throughout axonal retrograde transport." And I looked at their citations accordingly and it's just reviews and other toxins.
Josefina (J): I have a question for you [Lawrence] or you, [Shui],…. p75… ummm.. endocytosis and transport… it's not… is it considered a signaling endosome?
Lawrence (L): That's a good question. What do you think [Shui]?
S: Yes? I think so. But I'm not convinced that the authors-
L: The question is what does it signal? How does it signal, what is it signaling? And the answer is that there's not a whole lot of information on this. But keep in mind, I have done work in this and others have done work in this. And I don't know that anyone ever really convincingly showed that a p75-specific ligand was responsible for any signal going retrograde. Having said that, I could have missed them, but um, the question is, what is it? And what we need, what we need for this is you need to isolate the endosomes in essence. So what's going on there? You just need to look at them.
S: I thought the proBDNF would bond to p75 and then it listed all the cell and endocytosis pathways, so in that sense it is a signaling endosome.
L: But is it the fact that it is bound to the p75 receptor in retrograde axonal transport to the cell body.. [turning to a project scientist "Pei"] you may know a paper that I don't and that's great.
Pei (P): Just one paper reported that.
L: Sorry?
P: Just the one paper, I remember that p75 maybe in the form of a [late] endosome carried that in that retrograde endosome.
L: How did they prove that? Do you remember?
P: I don't remember. I only remember that paper only reported that.
S: What do you mean 'that endosome?'
P: It's the [late] endosome
S: Oh *that's* signaling.
L: How does it do it? What did they say?
P: Just the staining or whether they use micro image.
L: Ok. It's a really important question and I think we are in a position to really to do a good job looking at something like that. But you [to S] want to look at a p75-specific ligand, and pro-BDNF is not necessarily a p75-specific ligand. And why is that? You don't know that pro-BDNF is stable…. You know that pro-BDNF actually retards some sympathetic neurons. And BDNF working through p75 negatively impacts the ability of neurites to fan out and it kills sympathetic neurons. So, very likely, there is data for that. *But*, do you know that it is only p75 and do you know that- do you know anything about

how it signals….[L references other papers for S to look at on BDNF]. So it is completely conceivable that BDNF acts through p75 to do something negative. I believe that, but how it does that is not so clear. So we have some things we can quickly look at [referencing papers]. But do we really know how and where p75-specific retrograde signaling occurs and what it does and how it does it? There isn't much information about it. But having said that, we now have these p75-specific ligands and we can certainly look at cultures and the patterns of traffic in neurons and we can ask what the consequences are for the well-being of the neurons… so the good news is that we can do that and study it in a way that, perhaps, wasn't so easy for others to do.
S: Ok, so here it shows [referring to a figure from Wang et al's paper] that CTB overlaps with TrkB, and TrkB overlaps CTB. And even before their stimuli condition, which is higher potassium, there is still a very low percentage… There, 15% of CTB is TrkB positive. That means, another 85% of TrkB is labeled – I don't know.
J: But that isn't that surprising to me because TrkB can be in many different… it may be surface, it could be recycling.
S: Oh, they are looking at the axon.
J: Still, from this early…
L: So, the problem with overlap is that you don't know how much there is.
J: Yeah
L: So overlap – it's the correct number, I'm sure – So there are three possibilities for the low number. [1] There just aren't a lot of TrkB there. [2] Not a lot of CTB which is internalized, and [3] not a lot of co-localization in the same compartment. They're arguing for the overlap being critical, but the actual amount of CTB that is taken in and the amount of TrkB, they're not so clear on that.
L: So you got it? So if they have an overlap, you need to have one and the other.
S: If you have the C [referring to a figure], then you have the vaso-level less than 10% of TrkB is CTB positive.
L: Yes, but you have to have TrkB inside and you have to have CTB inside to have an overlap.
S: Yes, but I think they are normalized by the endocytosed TrkB.
L: They're just talking about percent. They are talking about the percent of overlap, nothing more. It's not relative to low-K.
S: I'm confused, so I need help…
L: It's okay. I don't think this is a big point.
L: If you have more CTB in the cell, then the chance of overlap is higher. Yes? If you have more CTB inside the cell, then the chance of overlap is higher. Yes? So, when you report out the degree of overlap, you can't talk about anything more than that single thing. If you change it with high-K, that's great! The question is, did I change it with high-K 'cause I changed the trafficking [of molecules that were already] within the cell, or did I just bring more stuff in?
S: Oh.
L: If more is inside, the chance for overlap is higher. If less is inside, then it is lower.
S: So you think the data doesn't differentiate?
L: I don't know what it is saying. It's just overlap. It doesn't tell me anything but that.
S: I thought that all the purple means it is endocytosed CTB.

L: If you tell me the percent co-localization changes, that's very interesting. But if you tell me there is more purple here, than here, and more green, here than here, all I would say is there's more! The chance that two things come together goes up if the amount of each goes up!
S: You think it is just randomly coming together?
L: No I don't! No, I'm just saying you can't conclude anything. The percentage of overlap is really interesting. But it is two things. It is whether they are in the compartment and how much there is. This only tells you how much is in the second compartment. It does not tell you how much there is. It does tell you that here. So is there a special compartment represented here that is not represented there? I don't think you could possibly conclude that. If you don't know the amount of the compartment because you aren't marking. Whatever you are doing with potassium effects both CTB and TrkB.
J: Unless you prove that it doesn't.
L: If you told me the amount of CTB inside the cell is constant with potassium. You would say 'oh! The increased co-localization means there is more trafficking coming into the compartment.' But both are changing. For me, this is a nuanced point which we will come to later, but for me overlap only means overlap. There is no denominator on overlap.
L: It is likely that it is the number of signaling endosomes reaching the cell body is responsible for trophic-yes. But are *these* signaling endosomes? Do we know they are signaling? Is there anything in the paper that says these guys signal? (pause) What are they staining? Are they signaling TrkB or p-TrkB?
S: Both?
L: Go back to the figure. I want to see the axon.
L: Go to the first slide. That is TrkB. I believe you can load the endosome with TrkB. I believe that. But is it *p-TrkB*? Keep going back. What are the other figures?
S: p-TrkB. I don't think-
L: It's TrkB.
S: I don't see any.
L: Well why not? Well wait a minute. Excuse me, [looking at Shui]. Here's the discussion. It's likely it that it is the number of signaling endosomes reaching the cell body that is responsible. Right. So write a paper about signaling endosomes and not one about an endosome that takes TrkB. How do I know that these are not endosomes that contain a little bit of TrkB? If they contain p-TrkB don't you think they would have stained for it? Wouldn't you have stained for it? How do I know that this isn't just taking TrkB surface receptors and shoveling them back into the cell body to be turned over...
L: So I sat there thinking, "How can we rescue Shui's project?" And I thought of a couple of things. First was, we need physiological meaningful stimuli. By the way, if you think about the biology of this project... And I really like the paper. I think it is a great paper, it is just misleading. What they are telling us that this guy here [the neuron] is only talking to himself. They're saying that if I activate this guy [the neuron], I can activate the receptors and get them to come back to the cell body, regardless of what goes on in the target. That's nonsense.
S: Well, (unclear, possibly "I don't know about that")…
L: That's a tumor! That is a tumor cell! That is what tumors do, they talk to themselves. They ignore their neighbor and talk to themselves! So there makes no sense in circuit

biology to have a neuron talk to itself and ignore its target. It makes absolutely no sense whatsoever. And I can tell you with the biology of growth factors is the size of the target is proportional to the trophic competency and that the amount, the concentration of released Nerve Growth Factor is proportional to the trophic competency and that the percent retrograde transport of the neurotrophic factor is proportional to the trophic competency. [Ying Yue] has made this very clear. She's done this antrogradely for BDNF and it is very clear. So, *this* [growth factor] says, "guys, just forget about the target! It's meaningless. Just stimulate this neuron and everything is going to be fine." So they don't prove that the endosomes can signal. This is the empty endosome theory. So where's your project fit?

L: The endosomes we are looking at require at least one molecule of the neurotrophin to be here to keep that process going on. That's the argument. Why? Because there are phosphatases out here that are incredibly active. And trying to kill the signal… You want to basically to kill, constantly attack that TrkB activated receptor to keep it turned off unless there was some active signal principle going on here. Right?

P: Couldn't there be- I've heard some tyrosine receptor it can- dimerization can induce autophosphorylation.

L: It can. And if overexpress TrkA by two or three-fold-

J: Yeah

L: It isn't that the NGF has some special meaning. The only meaning it has is to dimerize the receptor. But you either have to massively increase the concentration of the Trk receptor to do this or you have to keep a little NGF around.

P: Or it can just induce a shift of-

L: If you could keep potassium. If you depolarize the cell and it could continually beat on that endosome, only then it is a problem... We know in this experiment you had to get TrkB to the surface to activate it.

P: Yeah.

L: I don't know why. Maybe it was the local concentration of it… The question is, would potassium work on this system? And I think not. And here is the reason. There is a fundamental piece of the biology and you've got to target. The only reason for you to limit is to have a target. If you could keep yourself alive, you don't need a target.

P: I just guess maybe it isn't interested in clustering the TrkB receptors.

L: Sure!

P: It might want them to go inside-

L: Sure, sure, sure! So imagine you have TrkB sitting in a compartment here. I think it even alluded to the GLUT1 transporter. GLUT1 is this guy that pops up when he senses signals. It pops receptors up to the surface… So if activity may cause these receptors to sit here and pop up to the surface and then occupy a domain in which they are clustered together very tightly. And that would be very transient cause what you would expect it to do is pull them back down in an endosome or two… So when you [to Shui] tell me you get Trk activation for five minutes, I know it is not a signaling endosome. Because, by definition, a signaling endosome signals all the way into the cell body. So [Josefina] what do you think?

J: I agree! The p-TrkB signal doesn't die in other, um, plots I've seen from other people. They show, 30 minutes later they are still-

L: Well we could isolate endosomes from siatic nerve or on it. Their kinase activity can translate to an artificial substrate *in vitro* so they signal. So I think they've done a great job. I think is a really cool paper. Because what it says is that activity is important for this: for increasing the receptivity to the BDNF sitting out there, which then binds and keeps the signaling endosome on.
S: And the p-CREB tells you its signal can actually reach the cell body?
L: Where is the p-CREB signal?
S: After adding the-
L: Where is the p-CREB in the cell body? In this paper?
S: Um… in the middle?
L: In [Ying Yue]'s paper, yes. In [Zhu]'s paper, yes. I don't see it in this paper. *That* p-CREB (nodding at paper) is from the dish. They harvest the whole dish. They show you CTB in the cell bodies, they don't show you signals in the cell bodies. (pause) So it's a great paper in many ways.
S: Does the western plot count?
J: They didn't know.
P: No, no.
L: Not unless they harvest the whole culture, no.
P: (unclear) maybe in chambers-
L: It's five minutes.
P: Yeah.
L: It's all five minutes.
P: What if they did that in chambers?
L: If you did it in the cell *body* side of the chamber, *yeah*!
J: So p-CREB may have absolutely nothing to do with endocytosis.
L: Yeah. They didn't show you p-ERK or p-TYR, but anyway you can't- so think about it: they're stimulating for five minutes. They're harvesting for western plots… and they're waiting two hours to image.
J: That is a long time.
L: So, my comments were (pause) uh. This is the case of the empty vs. signaling endosome. This is the empty endosome. Well, I shouldn't say that. It is the *mute* vs. the signaling endosome. So I could be wrong, I could be totally be wrong, but this gives you then- and I really like the paper, but it says look: what the presynaptic neuron is saying, "I'm listening! Look, I'm *really* listening to my target. Are you out there? And I'm listening with my TrkB receptors, but I'm expecting you to give me some information. So I am going to keep listening as long as I am active as long as I am active. My listening is going on for ever and ever. And I'm an active axon. I'm going to be active and I'm going to keep putting my TrkB receptors out there. And soon as you have got some BDNF for me, I'm going to change. As soon as you get some p-TrkB back to me in the cell body, I am going change my genome and respond." And, by the way, [Josefina], it could be that this TrkB is enough to do some work in the axon terminal. It could be that the activated TrkB in the terminal is strong enough to signal through important modified proteins, protein synthesis, but this guy is *on*. He is revving *constantly*. I don't know, once per second or five times. He is *listening*. He's making TrkB come out here. So there's a conveyor belt of these endosomes coming in but they're not going to make a difference until they listen to the target.

L: So [Shui], that's the thing you should focus on, and you should use some of these tools and have fun with that! Right? So the argument would be that activity alone will not deliver a signal, or at the very least, a very weak signal. Whereas activity plus BDNF does. And you'll probably have to go over the same territory, but not so much. And then the question is, what is the physiological– (sigh) I really don't know. The worry that I have is the *physiological* signal you are trying to deliver is still too crude. I mean, I'm not disputing anything you are saying. I just want to make sure we're not just driving these neurons crazy with too much current, you know what I am saying? So how do we do that gently? And by the way, high potassium is a pretty big deal. I mean, that's like *whoa*! That's like a tsunami hit the cell *pow*! It's like being punched, right? (laughs) (unclear) But the idea that it is just *so* powerful. So the question is, what is the right thing to do? So the paper, the work that you do would be more valuable in the context of, "Oh I see. I've got a neuron that is being stimulated in a very gentle way. There's a certain amount of p-TrkB already there. At least there was when there was low potassium. That's very very nice. But that means nothing unless there is BDNF being handled in the axons, in terms of signaling. So think about that. Let's think about a physiologically meaningful stimulus…

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