THE CASE OF THE TRIGGERED MEMORY: SERENDIPITOUS DISCOVERY AND THE ETHICS OF CLINICAL RESEARCH

by

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Abstract

Should researchers take advantage of unexpected opportunities to make valuable discoveries when these opportunities arise in the context of research involving human participants? The pursuit of knowledge sometimes requires human beings to participate in research as the subjects of study. This is particularly the case when it comes to the pursuit of knowledge about the brain. In this dissertation, I consider the potential value of serendipitous discoveries in the context of clinical research involving humans, with a narrow focus on deep brain stimulation (DBS) – a technology that enables clinician-researchers to access and manipulate the living human brain.

Along the way, I accomplish three goals. First, I provide an account of serendipitous discovery in science. Serendipity consists of three elements—chance, sagacity and a valued outcome—that come together in a single process of discovery. Second, I apply my analysis to a case of potential serendipity in early phase medical research involving humans. Third, I explore the epistemological and ethical implications of both the analysis and its application. Serendipitous discoveries, for instance, are made by members of scientific communities, rather than by individuals in isolation. Thus, features of communities can enhance or constrain the making of serendipitous discoveries. Specifically, I argue that communities that perceive the unexpected as potentially valuable, that support the epistemic agency of their members, and that encourage the sharing of knowledge, foster serendipitous discovery.

I closely examine a recent case from clinical research with DBS—the case of the triggered memory—as a case of potential serendipity. The tripartite account of serendipity I articulate provides a lens through which I draw out several epistemological and ethical implications of pursuing serendipitous discovery within the context of clinical research, when human participants in research are the source of unexpected observations. In conclusion, I propose recommendations for pursuing serendipitous discovery in clinical research without compromising ethics.

List of Abbreviations Used

DBS	Deep Brain Stimulation
PD	Parkinson's disease
AD	Alzheimer's disease
REB	Research Ethics Board (Canada)

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Chapter 1 – Introduction

In this dissertation I accomplish three goals: I provide an analysis of serendipitous discovery in science; I apply that analysis to a case of potential serendipity in early phase clinical research involving humans; and I explore the epistemological and ethical implications of both the analysis and its application.

1.1 The Problem

The United States recently declared a national funding initiative directed toward furthering our knowledge of the brain – the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. According to proponents of the BRAIN Initiative, "the human brain remains one of the greatest mysteries in science and one of the greatest challenges in medicine."[1] The initiative intends to accelerate "the development and application of innovative technologies, [so that] researchers will be able to produce a revolutionary new dynamic picture of the brain…[l]ong desired by researchers seeking new ways to treat, cure, and even prevent brain disorders."[2]

The BRAIN Initiative reflects a theme in contemporary society, emerging from recently developed advanced technologies used to study and to intervene in the functions of the human brain. The theme reflects a strong desire—an imperative, I would argue—to learn as much as possible about the brain through the use of advanced technology. This imperative is accompanied by both a perception that we have much to learn about the brain and the anticipation that knowledge gained by studying the brain will have valuable outcomes for

[1] Retrieved 20 July 2015, from http://braininitiative.nih.gov/about.htm#B.
[2] Ibid.

medicine and for society as a whole. Among the advanced technologies of interest is deep brain stimulation (DBS), an intervention that uses electrical stimulation to modulate neural activity through electrodes implanted deep in the brain.

But even valuable knowledge cannot come at any cost.

When the human brain is the subject matter, human beings are tools of study. More specifically, when a better understanding of how the human brain functions is the goal of research, living human beings will be required to participate in at least some of that research. Some of the new technologies being used for studying the brain are fairly benign, but other technologies—such as DBS—are invasive, and the neurosurgical procedures involved in the use of those technologies are risky for human beings. The epistemic imperative to learn more about the human brain through the use of advanced technology is only acceptable as a guide to research alongside an ethical imperative, to conduct only ethical research with human participants.

There are numerous issues that can be raised in regard to this intersection of epistemic and ethical imperatives in clinical research intended to produce knowledge about the human brain. In this dissertation I look at a specific instance of one such issue. The issue I am concerned with, broadly speaking, is how the potential value of knowledge that can be gained from research on the human brain should be weighed against the risks undertaken by the participants in that research. More specifically, I look to an instance of potential serendipity in DBS research for insight into how potential value can and should be weighed against risks to research participants. Serendipitous discoveries represent valuable outcomes that emerge in part by chance. As a unique and yet informative category of discovery, serendipitous discovery provides

a lens through which I illustrate how the goal of generating valuable knowledge with clinical research may conflict with accepted criteria for the ethical conduct of clinical research.

In the following section I provide a brief introduction to serendipity and the tripartite account I argue for in this dissertation. In section 1.3 I give some reasons why serendipitous discovery offers a unique and revealing perspective on how discoveries are made, with implications for philosophy of science and the ethics of clinical research. In section 1.4 I provide an overview of the structure of this thesis.

1.2 Serendipity

Serendipity is a label chosen to differentiate some chance discoveries from discoveries that are merely lucky. For example, Alexander Fleming was awarded a Nobel Prize for his role in the serendipitous discovery of penicillin—this suggests that, while his originating observation was made by chance, Fleming was thought to be more than lucky for making it. Serendipity identifies a perception that a discovery has occurred at the intersection of chance and insight or, in the terms offered by Horace Walpole when he first coined the term, "accidents and sagacity" (Walpole, [1754], p. 408). Generically defined as a kind of perceptiveness and wisdom, sagacity seems to represent a kind of knowledge-producing talent or skill that makes discoveries out of accidents.

Serendipity is also a normative concept. In science, attributing sagacity to someone by categorizing a discovery that began with her unexpected observation as serendipitous indicates an evaluation or appraisal of that person. Sagacity denotes recognition of that person's insight, despite the fact it was by chance she became involved in the processes leading to a valuable scientific discovery: she nevertheless contributed evidence that enabled that valuable discovery to be made. Researchers who exploit an unexpected or chance observation as an opportunity

for making a valuable discovery, are granted epistemic credit for their contributions. The assignation of the category of serendipity to describe a discovery thereby reflects the values of an epistemic community, as well as the epistemic agency of the researchers involved. I will show in the following chapters that although narratives of serendipitous discovery in science assign praise for sagacity to individual observers, discoveries are made at the level of scientific communities. Close examination of the nature of the three elements of serendipity and their interaction within a process of discovery reveals that each element is contextual, and that context is the relevant epistemic community. Chapter 2 describes the tripartite account of serendipity I offer and its implications for understanding serendipitous discovery in science.

I further argue that because social-epistemological factors—features of an epistemic community—are a large part of what makes serendipity happen, communities that have certain features are more likely to foster serendipitous discoveries. I argue that the features of such fostering communities include: encouraging members to perceive unexpected observations as opportunities for the production of knowledge; supporting the agency of community members; and maintaining the means for members to easily access more and varied knowledge. These views are defended and explicated in Chapter 4.

1.2.a A Tripartite Account of Serendipity

The primary contribution this dissertation makes to the serendipity literature is my argument for a tripartite account of serendipity as the confluence of three elements--chance, sagacity and a valued outcome—in a single process of discovery that is essentially context-dependent.

According to my tripartite account, the three elements of serendipity interact within a single process of discovery. All three elements are contextual. Context determines what counts

as chance and what is perceived by chance. Context also determines who makes chance observations and who has the agency to both follow them up and be recognized for making them. And, context determines which discoveries are valuable and what stories get told about their making. Thus, all three elements of serendipity—chance, sagacity and a valued outcome—may be present in a given scenario, and yet, without the right context, a serendipitous discovery may still not come about as a result of a chance or unexpected observation. Chance, sagacity and valuable outcomes do not exist in the abstract, but as categories they describe the three elements of the resulting configuration, when certain kinds of events, people and values come together in a process of serendipitous discovery.

In this dissertation, my focus is on serendipity as it occurs in the context of clinical research. For my purposes, clinical research constitutes a subfield of scientific research. Thus serendipity, in this analysis, denotes a process of scientific discovery that includes the three aspects of chance, sagacity and a valued outcome (the discovery itself). When serendipity plays a necessary or causal role in the making of a discovery, that discovery can be called a 'serendipitous discovery.' While serendipity is commonly associated with discoveries of greater-than-average value, this is not a necessary element of serendipity. However, insofar as the term 'scientific discovery' denotes something of value to science, serendipity in science *is* associated with scientific value.

1.3 Serendipitous Discovery

The tripartite account of serendipity I offer provides a lens through which to analyse serendipitous discovery in science and clinical research. My analysis has implications for philosophy of science and the ethics of clinical research.

1.3.a Philosophy of Science

As a contribution to philosophy of science, I intend this dissertation to answer the following question: is serendipity a particular kind of discovery, and if so, can its necessary conditions be described?

The tripartite account I offer suggests that while serendipitous discovery is a particular kind of discovery in science, its analysis reveals characteristics of scientific discovery in general. Serendipitous discovery is often interpreted in the literature to imply that valuable discoveries are made by individual researchers, perhaps geniuses, who are free to pursue their own epistemic goals. In contrast, the tripartite account of serendipity I offer affirms a social-epistemological description of serendipitous discovery. Through the lens of the tripartite account, serendipitous discoveries are shown to be made not by individuals in isolation, but by members of epistemic communities—especially those communities with features that foster serendipity.

1.3.b Ethics of Clinical Research

> An experiment is ethical or not at its inception; it does not become ethical *post hoc* – ends do not justify means. (Beecher, 1966, p. 372)

Social-epistemological factors make up only one part of the considerations at hand when assessing potential value in the context of clinical research. It is important to critically examine the ethical implications of taking advantage of unexpected observations to produce knowledge during the early phases of clinical research, when human participants are involved. I intend to answer the following question relevant to the ethics of clinical research: when is *potential* serendipity valuable enough to warrant the attention of clinical researchers and, consequently, the use of human participants to make a serendipitous discovery?

The value of clinical research is a complex standard to assess. Although it is widely accepted that research with human participants must be valuable to be ethical (Freedman, 1987; Emanuel, Wendler, & Grady, 2000), what is considered valuable research is a matter of little definition and much debate (Borgerson, 2013). Jonathan Kimmelman points out that, "how investigators, policy-makers, and ethics committees should *prospectively* assess a[n early phase] study's value remains virtually unaddressed" (Kimmelman, 2010, p.90). While clinical research constitutes a subfield of scientific research, the value of clinical research cannot be measured only as epistemic value. When the potential epistemic value of conducting research is being weighed against the risks to human participants, assessments of value must take more into consideration than the potential value of the projected epistemic outcomes.

Because serendipitous discovery arises by chance, then, it raises the question of how to prospectively assess the potential value of a projected outcome. In clinical research, such prospective evaluations are used to justify the selection and inclusion of human participants in clinical studies. Because that projected value is weighed against the risks to participants, it is important to have a framework for assessing when potential value may be said to be sufficient to warrant those risks. This is particularly important in contexts such as first-in-human research with DBS technology, where both the projected value and the risks of an invasive procedure are potentially great. Potential serendipity in clinical research presents an extreme case in respect to this issue, but one that offers valuable insights into the epistemology and ethics of clinical research that studies and intervenes in the functions of the human brain.

1.4 Map of the Dissertation

Chapter 2, *Defining Serendipity*, provides a literature review and analysis of the concept of serendipity. I show first that accounts of serendipity in the literature typically, erroneously

focus on only the insight and actions of a particular individual, or fail to fully elucidate how the unexpected observation made by that individual becomes categorized as serendipity. I then argue for a tripartite account of serendipity, wherein serendipitous discovery consists in the confluence of three elements—chance, sagacity and a valued outcome—within a discovery process. The valued outcome has seldom been made explicit as a third and necessary element in serendipity, but once it is, several features of serendipity become clear.

The fact that a valued outcome is an essential element in serendipity highlights the role of the community in making serendipitous discoveries. Epistemic communities determine when opportunities for chance observations arise and can be taken advantage of; epistemic communities determine what kind of work needs to be done for such observations to be taken up into processes of discovery; epistemic communities determine which discoveries will be valued, and when. Thus, the epistemic community influences not only the valued outcome, its content and probability, but also the content and probability of chance and sagacity in each instance of serendipitous discovery.

Further, I argue that the valued outcome must first be determined before serendipity can be identified. This has several consequences. First, the category of serendipity can only be applied retrospectively. Second, not everything that happens by chance and sagacity will lead to a valued outcome—the valued outcome differentiates serendipity from less fortunate accidents and mistakes. As well, an observer does not earn the status of sagacity unless she makes a contribution of knowledge to a community. Thus, the status of chance and sagacity as serendipitous is also dependent on a valued outcome. Finally, what kinds of outcome are valued by a community determines what kinds of chance observations and what kinds of sagacity lead to discoveries in that community. For example, in the scientific community, random events without

generalizable explanations will not give rise to serendipity, but chance events that reveal unknown causal relationships might.

The latter half of Chapter 2 provides nuanced descriptions of chance, sagacity and the valued outcome. Chance, as I will show, is related to the processes underway and the focus of attention of observers at the time. Further, community processes and values affect which chance observations might be taken up by observers and their communities. Sagacity is a more complex concept in relation to serendipity and requires some unpacking. The literature is especially rich in regard to sagacity, but provides diverse and sometimes irreconcilable accounts of its nature. Therefore, I spend time in this chapter reviewing and consolidating the various accounts. Sagacity denotes both a rhetorical category of appraisal and recognition of the agency of the relevant individual(s) that enabled the completion of a discovery process. Examining sagacity through a lens of epistemic agency demonstrates the importance of community, trust and epistemic action to serendipity. Finally, the valued outcome allows for an instance of serendipity to be identified as such. The confluence of all three factors required for serendipity, however, may not occur within a lifetime or community, but may be extended across time, individuals and communities.

Chapter 3, *Paradigms of Serendipity*, describes and discusses two paradigmatic examples of serendipity from the history of medical research. The story of Barry Marshall traces the discovery of *H. pylori*, a bacterial cause of stomach ulcers. Alexander Fleming and the discovery of penicillin is the second example. Similarities shared by these two processes of discovery illuminate the strengths of the tripartite account of serendipity as a lens for analysis, and affirm the descriptions given in Chapter 2 of chance, sagacity, and valued outcome. Details from the processes leading to each discovery highlight the contingency of the connection

between an unexpected observation and a valued outcome and the role of the community in enabling serendipitous discovery.

Using the tripartite account of serendipitous discovery as a lens, I examine how chance, sagacity and the valued outcome interact to identify each of the two discoveries described in this chapter as serendipitous. I also look to how the community in each case influenced the confluence of the three elements. Finally, I examine closely how the epistemic agency of Marshall and Fleming enabled them to play the roles they did in the process of serendipitous discovery for which they were awarded Nobel Prizes. In the discussion of the results of my analysis, I highlight important differences between the roles Marshall and Fleming played in their respective narratives of discovery. Employing the tripartite account, I use these differences to illustrate how serendipitous discoveries are made by members of scientific communities, rather than by scientists working in isolation.

Chapter 4, *Prospective, Potential Serendipity*, is an examination of the difference between identifying serendipity retrospectively and assessing the probability of potential serendipity prospectively. I look briefly to the philosophy of science for other accounts of serendipitous discovery, drawing primarily from Aharon Kantorovich. Kantorovich uses serendipity as an epistemological tool to explain how chance introduces novelty, enabling the progress of science. I refer to Thomas Nickles' approach to discovery to expand upon Kantorovich's claim that science nevertheless progresses rationally, and to further elucidate the role of communities in serendipitous scientific discovery. The epistemology of scientific discovery reinforces the importance of community and the valued outcome in understanding serendipitous discovery.

Moving away from the definitional account given of serendipity so far, Chapter 4 develops a probabilistic, causal account that provides tools for assessing the probability that

serendipitous discoveries will occur in a given context. From the literature, I draw on examples—from organizational theory, information science, computer science, and biology—of efforts to delineate methods for fostering serendipity in communities. These methods can be briefly categorized as: encouraging community members to perceive unexpected observations as opportunities for knowledge production; supporting the agency of community members; and improving and maintaining their access to knowledge. I discuss the relationship between these methods and the three elements that define serendipity. Some communities are more likely to enable the confluence of the three elements in serendipitous discovery than others. I describe some of the features of communities that foster serendipity, and explain how those features enable the confluence of chance, sagacity and valued outcomes.

Finally, Chapter 4 provides a description of the kind of insight and epistemic action required of individual and communities of scientists who wish their unexpected observations to be taken up into a process of serendipitous discovery. Specifically, I use Peter Achinstein's (2001) concept of potential evidence. The value of potential evidence to science and to scientists lies in the (perhaps eventual) verification of the hypothesis it is evidence for; until then, it remains potentially valuable. Further, the projected value of an unexpected observation—the content of the observer's insight—is not always the same as the valued outcome. For example, Fleming perceived that the mould he unexpectedly observed had potential value, but he did not perceive its ultimate value—the revolutionary change it would bring to the practice of medicine. The norms and values of an epistemic community determine the timing, location and content of the valued outcome, and thereby determine the ultimate value of the potential evidence. I propose collateral value as one way to describe the value of potential evidence in instances of potential serendipity in science.

Chapter 5, *The Case of the Triggered Memory*, applies the framework of collateral value to a case in contemporary experimental neurosurgical research. I describe the case in some detail there, but briefly here. In 2003 in Toronto, Canada, a neurosurgical team led by Andres Lozano made an unexpected observation when they triggered a memory in an obese man undergoing neurosurgery to implant DBS technology as an innovative treatment to control his appetite (i.e., the obesity-DBS protocol). This observation has already been called serendipitous by the media and by some researchers.

I describe the case of the triggered memory, providing details regarding: the justification for the obesity-DBS protocol described in the case report; the response to the observation of the triggered memory; and the results of the research. The case of the triggered memory presents three elements, an unexpected observation, researchers who have exercised epistemic agency to produce potential evidence, and a projected valuable outcome. As such, the case of the triggered memory is a case of potential serendipity—it could potentially initiate a discovery process in which the confluence of all three elements would occur. Further, the community in which the case occurs shares features with communities that foster serendipitous discovery.

I claim in this chapter that serendipitous discovery does not necessarily occur by leaps and bounds, but can just as well be fostered by progressive clinical studies and by attending to possibilities for collateral value. I consider in particular the probability that the obesity-DBS protocol, as amended in response to the observation of the triggered memory, will or has already contributed to the process of discovery represented by the new direction of research taken on by the Toronto team. The new research direction intends to replicate the observations of memory enhancement in the original obese participant in participants who have been diagnosed with Alzheimer's disease (AD). I present an argument in favour of

minimizing the epistemic distance between the research involving the obese participant who was the source of the unexpected observation and any inferences made about what effects the same procedure may have on different people.

Chapter 6, *The Ethics of Serendipity in Clinical Research*, examines the implications of potential serendipity that arises in clinical research. Epistemic value is not always sufficient to warrant changes in protocol of the type required to create the kind of evidence that researchers will likely be recognized for having contributed. I demonstrate that whereas the obesity-DBS protocol was designed with therapeutic intent, the amendments made to that protocol in response to the unexpected observation of the triggered memory introduce novel, epistemic aims. This shift in epistemic intent has implications in regard to several accepted criteria for ethical clinical research (Emanuel, Wendler, & Grady, 2000).

I argue that the amendments made to the obesity-DBS protocol in response to the observation of the triggered memory ought to have been subject to independent research ethics review (as all ethical clinical research must be). The shift in epistemic intent shifted the purposes and values of the original study, the selection criteria for participants in the study, and the ratio of risk to possible benefit. These shifts in turn were sufficient to warrant a new REB review of the proposed, integrated study (or of a new study altogether). The study in which the obese participant ended up participating was different in significant ways from the study to which he originally consented.

The conflicts liable to occur between the epistemic and ethical goals of clinical research in instances of potential serendipity do not necessarily diminish the community of clinical researchers' ability to foster serendipitous discovery. In the concluding sections of Chapter 6, I

consider methods for pursuing potential serendipity in clinical research without compromising ethics.

Finally, Chapter 7 provides a summary of the key arguments presented in this dissertation. I finish by offering a quick review of several implications of those arguments and their conclusions for serendipity theory, philosophy of discovery and ethics of clinical research.

Chapter 2 – Defining Serendipity

"Serendipity" is a term invented in 1754 by Horace Walpole, in a letter written to a friend. It denotes, according to Walpole, the kind of discovery that is made "by accidents and sagacity, of things [the discoverers] were not in quest of" (Walpole, [1754], p. 408). In pointing to accidental discovery, Walpole meant to highlight what many have called a 'Eureka' moment, after the tale of Archimedes in the bath: an unexpected but particularly delightful event, experienced by collectors and researchers who find things they were not looking for but that nevertheless turn out to be valuable. By "sagacity" Walpole meant a kind of wisdom; the Oxford English Dictionary online defines the adjective "sagacious" as "having or showing keen mental discernment and good judgement; wise or shrewd."[3] Thus, in simplest terms, serendipity occurs when a discovery is made as a result of both chance and sagacity.

Robert Merton and Elinor Barber published a hefty volume devoted to the term, its history and its use, in 2004,[4] titled, *The Travels and Adventures of Serendipity: A Study in Sociological Semantics and the Sociology of Science*. Tracing the development of serendipity as a term in the English language, Merton and Barber note that it resists "precise interpretation"(Merton & Barber, 2004, p. xiv). Ultimately, they conclude that serendipity is "always about discovery and always what Walpole called 'happy accident,' but the exact mixture of wisdom and luck … varies as the word is employed in different contexts" (Merton & Barber,

[3] http://www.oxforddictionaries.com/definition/english/sagacious. Accessed 18 July 2015.

[4] Note, the volume was effectively completed long before (in 1958); the lag between completion and publication was intentional, as it seems the authors had decided not to publish it after all. The word 'serendipity' did not become so popular until later – before 1958, the word had been found in print only 135 times by Merton. Between 1958 and the 1990s the word surged in popularity, found in the titles of books, stores, films and in newspaper advertising and articles. As well, the complete but unpublished book was cited in introductions to reprints of Merton's book and in articles about serendipity by colleagues of his who knew of its existence. Finally, the demand for the book's publication resulted in just that, in 2004.

2004, p. xiv). The latter quotation, however, implies a third element in addition to accidents/luck (what I refer to as chance) and wisdom/sagacity: the nature of the discovery itself. That is, what I call the "valued outcome" is what makes the accident turn out to be a happy one and affirms the observer's sagacity.

In this chapter I argue that chance, sagacity and a valued outcome are three logically necessary elements that define what counts as a serendipitous discovery. Theories of serendipity in science that fail to explicitly include, or ignore, one or more of these elements either imply the others, or are incomplete. Further, insufficient emphasis on the importance of the valued outcome in identifying serendipity minimizes the importance of contextual factors in enabling serendipitous discoveries. In particular, accounts of serendipity in the literature tend to focus on the role of the individual as discoverer. The tripartite account I offer shows instead that serendipitous discovery in science occurs at the level of the scientific community. The scientific community structures all three elements involved in serendipity as well as creating the conditions for the confluence of the three elements in a process of discovery. Further, because the (valued) outcome can only be determined once the discovery process is complete, the status of a chance observation as serendipitous and the status of the observer as sagacious are only known in hindsight. I conclude by providing detailed definitions of chance, sagacity and valued outcome that take into account the social-epistemological context in which their confluence occurs.

2.1 Argument for a Tripartite Account of Serendipity and Survey of the Literature

The serendipity literature is multi-disciplinary and offers diverse approaches to serendipity. Some accounts of serendipity focus on personal experiences or on serendipity as a source of discovery in a particular field. The former are mostly collections of anecdotes interspersed with theory, meant for popular interest (Kohn, 1989; Meyers, 2007; Roberts, 1989). The latter attempt to compare serendipity as it appears in different fields, offering theoretical frameworks for future study (Merton & Barber, 2004; Morley & de Rond, 2010).

Other accounts focus on serendipity as an illustration of human creativity, or as a result of certain behaviours. Those who wish to understand creativity in science examine serendipity from the perspectives of cognitive or psychological theory and research (Austin, 2003; Simonton, 2004; Thagard, 2011). In other empirical research, interviews are conducted with academics and other information-seekers who encounter serendipity in their work (Fine & Deegan, 1996; Foster & Ford, 2003; Makri & Blandford, 2011; McBirnie, 2008). Alternatively, the experiences and career paths of scientists who have experienced serendipity are specifically researched and compared (Campanario, 1996; Mcbirnie, 2012; Stoskopf, 2005).

In general, serendipity can further be seen as either a phenomenon that happens during the course of research or as the ability or art expressed by someone in response to an unexpected observation (Merton, 1948; van Andel, 1994). Authors of accounts of serendipity seem to choose one perspective over another, intentionally focussing on either (subjective) perceptions of serendipity or on the role serendipity has played in the (objective) progress of science (Friedel, 2001; Kantorovich, 1993; Makri & Blandford, 2012a, p. 16; Simonton, 2004).

2.1.a Variations on Walpole's Theme

Most accounts of serendipity reference Walpole's coinage of the term "serendipity" (Silver 2015), offering a definition of serendipitous discovery with two necessary elements: chance and sagacity. For example, accounts of serendipity by historian of technology Robert Friedel (2001), organizational theorist Mark de Rond (2014), and sociologist of science Robert Merton (1948) draw on Walpole's formulation of serendipity as "accidents and sagacity," although they differ in the emphasis they give to each of the two characteristics.

Friedel (2001) focuses on the importance of chance to science that he believes serendipity represents. He offers a breakdown of serendipity in science into three kinds: Columbian, Archimedian and Galilean. As with Columbus' so-called discovery of America, Columbian serendipity occurs when someone accidentally finds something of value while seeking something else (Friedel, 2001, p. 39). Whilst seeking a path to the Far East, Columbus stumbled upon the New World instead: a discovery of equal if not greater value than the one he had originally intended.[5] Archimedean serendipity occurs when someone is looking for the thing they have found, but have found it in an unexpected place (pp. 39-40). In the classic tale, Archimedes is looking for a way to test the gold content in a crown when he took a bath. Recognizing that his body had displaced the water when he got into the bath, the method for measuring the volume of the crown became apparent to him. He did not, however, expect to find the solution to his problem in the bath. Finally, Galilean serendipity is no accident, in the sense that Galileo found just what he was seeking when he turned his telescope to the sky, a better view of the stars, but

[5] Walpole's definition of serendipity as "accidents and sagacity", then, falls under Friedel's definition of Columbian serendipity. As Friedel himself points out, however, even the examples given by Walpole as well as the original story of the Princes from which he claims to have derived the term are not well described as "accidents" (Friedel, 2001, p.38).

the value of what he saw was far more than he had originally expected it to be (Friedel, 2001, p. 40). For Friedel, even though Galilean serendipity is not accidental, "it seems impossible to fully comprehend the role of serendipity in science and technology without including it" (Friedel, 2001, p. 40). Thus, serendipity highlights the role of the unexpected in scientific progress in Friedel's account—without surprise, there would be no science, he suggests.

De Rond (2014) has examined serendipity for its role in making some organizations more innovative than others. In contrast to Friedel, de Rond posits that while serendipity indeed arises by chance, what makes it serendipity is the sagacity involved. He looks to exemplars from the history of science to show that, in every case, a particular capability has been exhibited: "Rather than being synonymous with chance, serendipity results from identifying 'matching pairs' of events that are put to practical or strategic use … serendipity thus describes a *capability*, not an event. It follows that human agency, and not probability, is properly the focus of attention" (de Rond, 2014, p. 1). For de Rond, serendipity is the making of a meaningful connection; the fact that the connection was unexpectedly made explains the specific role of serendipity in innovation.

Merton (1948) penned the account of serendipity most commonly referred to (after Walpole's) in the literature. Merton offers the "serendipity pattern," which occurs whenever an, "unanticipated, anomalous and strategic datum exerts a pressure for initiating theory" (Merton, 1948, p. 506). By an *unanticipated* datum, Merton means that the context of research activity in which the datum is observed is not directed toward the observation of that datum. The researcher is pursuing a hypothesis through empirical research, but the datum observed "bears upon theories not in question when the research was begun" (Merton, 1948, p. 506). Merton suggests that an *anomalous* datum is *surprising*, "either because it seems inconsistent with prevailing theory or with other established facts" (Merton, 1948, p. 506). Merton considers the

datum to be *strategic* insofar as "it must permit of implications which bear upon generalized theory" (Merton, 1948, p. 507). Given that Merton's pattern represents serendipity in terms of relations between theories and data, it may appear that he, like Friedel, focuses on chance (the data are "unanticipated" and "anomalous") and ignores sagacity. But the researcher is not absent from Merton's account.

Because the datum is surprising, it "provokes curiosity" in the researcher, who is then "stimulated" to try to "make sense of the datum" (Merton, 1948, p. 506). That is, the datum is anomalous in comparison with prevailing theory and knowledge, but it is the observing researcher who possesses that knowledge and is familiar with that theory who does the work of comparing her observations to what she already knows. While the datum is active in the sense that it provokes the researcher to do this work, the work requires the right researcher in order for it to be done. In this discussion of the relations between the datum and theory, then, Merton does not ignore the contribution of the observer. Thus, the element of chance, as expressed by a datum that is unanticipated and anomalous, combines with the element of sagacity.

Merton explicitly addresses this role of the observer when he describes the datum as *strategic*: "it must permit of implications which bear upon generalized theory" (Merton, 1948, p. 507). For Merton, this aspect describes what the researcher "brings to the datum" she observes (Merton, 1948, p. 507). While the datum exists in the world to be discovered, it requires the "theoretical sensitivity" of a sagacious researcher to see how that observed datum extends or modifies theory (Merton, 1948, p. 507). The researcher "explores further" and "makes fresh observations" to confirm her hunch about the datum's significance (Merton, 1948, p. 506). The datum, existing theory, and the researcher together determine whether the datum is perceived as unanticipated, anomalous and strategic. In other words, the datum *unexpectedly* confronts an observer, and the observer *sagaciously* responds.

Similarly, the element of sagacity is implied in Friedel's account that focuses on the importance of chance, and the element of chance is implied in de Rond's account that focuses on the importance of sagacity. In focusing on the chance element of serendipity, Friedel pays little attention to what sagacity may be when giving his definitions. Yet, he makes reference to sagacity as a kind of wisdom particular to serendipity as well. For Friedel, serendipity lies outside the bounds of normal science, and accordingly someone who correctly recognizes potential value in an unexpected observation must have a "mental capacity that goes beyond the obvious" (Friedel, 2001, p. 38). Thus, while chance defines serendipity and distinguishes the types of serendipity that occur in science, serendipity still requires a sagacious individual to come about, in Friedel's account.

As well, while de Rond appeals to exemplars from the serendipity literature to derive his definition of serendipity as a human capability, he chooses them because they exemplify the intersection of this capability with chance. It is not the capability itself that makes serendipity a particular kind of discovery but the fact that this capability is being exercised in response to an unexpected observation. De Rond and others who would favour sagacity in describing the constitution of serendipity, do not thereby eliminate the importance of chance even when they neglect or dismiss it. For instance, regardless of whether the original observation arose by chance, it remains important that a particular (sagacious) individual observed it. As de Rond emphasises, what is interesting about the making of the connection that happens in serendipity is that someone else, someone without the capability needed, would not have made that connection (de Rond, 2014, p. 14). Chance still plays an essential role in accounts of serendipity that focus on sagacity, as it is also a matter of chance that an appropriately sagacious individual made the relevant observation.

Accounts of serendipity that attempt to emphasise one element fail to do so without

implicating the other(s). When sagacity is emphasized, chance is still found to play an active role in differentiating that sagacity from the wisdom required for normal practice. As well, when chance is emphasized, sagacity still differentiates serendipity from other chance discoveries. Without sagacity, we are left with a chance discovery that any person could have made. Insofar as it is a distinct category for a particular kind of discovery, serendipity entails the intersection of chance and sagacity both.

2.1.b Valued Outcome – The Third Element

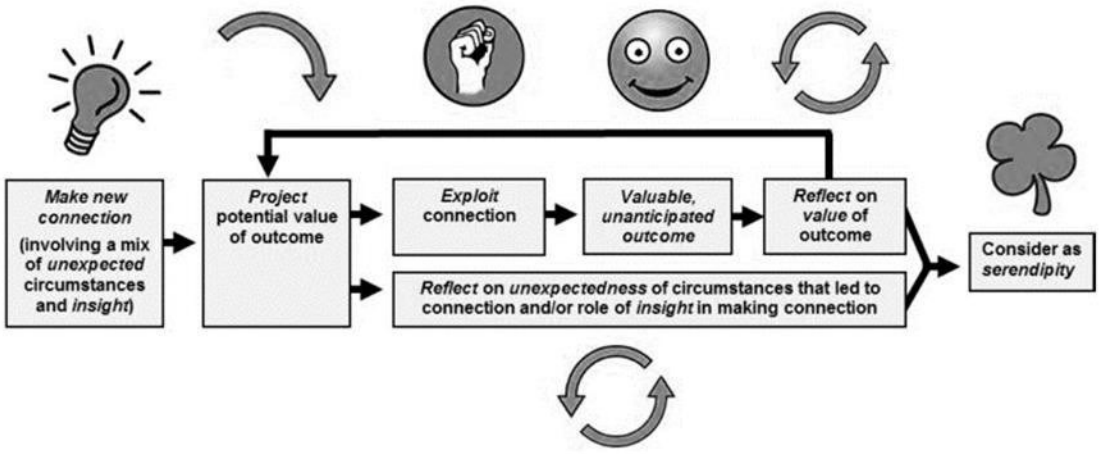
Recall that Walpole's definition of serendipity referred to two criteria, accidents (chance) and sagacity. Similarly, Merton and Barber appeal to luck and wisdom, but in their reference to happy accidents, as I have suggested, the third criterion of a valued outcome is implied. This third element is also necessary for defining serendipitous discovery in science, but is often either ignored or left out of definitions, if not descriptions, of serendipity in the literature. An exception is the account offered by Stephann Makri and Ann Blandford.

Makri and Blandford conducted an extended qualitative investigation into serendipity by conducting interviews with a number of interdisciplinary researchers and academics. From the data collected and their analysis, they created a process model of serendipity (see Figure 1 below). Makri and Blandford describe the process as, "*making a mental* connection that has the potential to lead to a valuable outcome, *projecting the* value of the outcome and *taking actions to exploit* the connection, leading to a *valuable outcome"* (Makri & Blandford, 2012b, p. 2, emphasis theirs).

This tripartite model includes the three elements of chance, sagacity and valued outcome as all necessary to serendipity. Chance is captured in the model by "unexpected circumstances" and an "unanticipated outcome." Sagacity is captured in several steps of the process, including the *insight* necessary to make a new connection, the *projection* of the

"potential value of the outcome," the *exploitation* of the connection to confirm that value, and the *reflections* required to perceive the confluence of factors as serendipity.

Figure 1 Makri & Blandford's process model (2012a, p. 7)



Makri and Blandford make the necessity of a valued outcome explicit by giving a process model of serendipity. The process of serendipity is only complete when its valued outcome has been determined. Further, as their model shows, serendipity is only perceived once all three factors have come together in a single process of discovery. This has implications for accounts that imagine serendipity to be captured by a "Eureka" moment of chance insight and realization: such accounts reduce serendipity to chance and sagacity only by ignoring the importance of the valued outcome. Further, this process model highlights the work that needs to be done after an observation is perceived as potentially valuable. Importantly, this model also explicitly acknowledges that the categorization of an unexpected observation as serendipitous is done retrospectively. By drawing out the process of serendipity into its steps, Makri and Blandford's model shows both the importance of the valued outcome to defining serendipity, and the fact that all three elements are inter-related throughout the relevant discovery process.

No definition of serendipity in science is complete without including these three logically necessary elements: chance, sagacity and a valued outcome. Just as sagacity may be implied despite a focus on chance, and chance may be implied despite a focus on sagacity, the third element, a valued outcome, may be implied by accounts of serendipity in science that recognize one or the other two criteria.

The accounts described above—from Makri and Blandford, Merton, de Rond, and Friedel—rely on a valued outcome for identifying an unexpected observation as an instance of serendipity. In addition, the accounts described above only consider examples of successful, serendipitous discovery in their survey and analysis of serendipity.[6] I argue this indicates that it is not enough for a sagacious individual to recognize the potential value of an unexpected observation for the completion of a process of serendipitous discovery. That observation must also be made in the right environment and taken up by the right epistemic community.

For instance, the "strategic" aspect of Merton's datum is related both to the insight of the sagacious observer and the content of that insight, which is a (projected) change in or extension of theory. It is more than "fortunate" for the researcher, as Merton suggests, when her "hunch" is proven correct and her pursuit rewarded (Merton, 1948, p. 506). "The serendipity pattern, then, involves the unanticipated, anomalous and strategic datum which exerts pressure upon the investigator for a *new direction of inquiry which extends theory*" (Merton, 1948, p. 507, emphasis mine). Thus, to be illustrative of the serendipity pattern, a discovery must go beyond the chance observation and the sagacious recognition of its potential value; it must actually obtain that potential value. What determines the value of the original

[6] Exceptions to this rule are Kohn, who writes specifically about missed opportunities that we know about from the history of science (Kohn, 1989), and Barber and Fox, who write about (almost) lost opportunities for serendipitous discoveries (Barber & Fox, 1958).

observation in a serendipitous discovery, in turn, is the outcome of that observation, the value of the discovery itself.

Merton's own example of the serendipity pattern illustrates the impact of a valued outcome on the perception of an originating, chance observation. The example he gives is from contemporary sociological research, wherein a researcher confirms a link between social relations and social perceptions because of a chance comment (observation) that he elicits from a research participant and that inspires him to investigate further (Merton, 1948, pp. 507-509) . The researcher who makes the observation is part of a project examining the social organization of a working class suburb in the United States, to understand why parents in this suburb seem to be more involved in social activities than other parents in other, similar suburbs. This researcher elicits an *unanticipated* response from a participant, that there are plenty of teenagers about, when in fact there are few teenagers in the local community.

Prevailing theory holds that social perceptions are determined either by a social framework, or by personal advantage. But in this case, the mistaken belief that there are plenty of teenagers about cannot be explained by the social framework, and there is no personal advantage associated with holding the belief. As such, the response is *anomalous*. The researcher seeks an explanation for the mistaked belief, which in turn calls into question assumptions about social perceptions. The participant believed there were many teenagers in the local community because she felt comfortable calling on any of several teenagers for her childcare needs. In this case, social relationships led to the formation of social perceptions. The unanticipated datum in this example guides the actions of the researcher, who perceives the *strategic* possibilities for that datum in relation to prevailing theory. At the end of the example, Merton notes the following:

> From the sociological viewpoint, then, this unanticipated finding fits into and extends the theory that "social perception" is the product of a social framework. It develops further the "psychology of social norms," for it is not merely an instance of individuals assimilating particular norms, judgments, and standards from other members of the community. The social perception is rather, a by-product, a derivative, of the structure of human relations. (Merton, 1948, pp. 508–509)

An important feature of Merton's example is that the anomalous datum made a contribution to sociological theory.[7] Had it remained a random utterance, or had no explanation or only an insignificant explanation been found (such as irrational, personal belief rather than social perception), then the original anomalous datum and its observation would have made no difference to sociological theory. Its observation would not have led to a discovery, or a valued outcome. Even though Merton's example concentrates on a singular observation (the datum) and on the insight and actions of a single individual (the researcher), the change that the datum made to sociological theory implies that the valued outcome takes serendipity out of the level of the individual and into the community—where the "sociological viewpoint" is located. Thus, it is the impact of the datum on prevailing knowledge at the level of the community that signals the completion of the serendipity pattern.[8]

Similarly, de Rond fails to explicitly include the valued outcome as part of his own definition of serendipity. The four examples of serendipity de Rond examines, however, are all

[7] In fact, the value of the serendipity pattern is determined by its influence on prevailing theory. The 1948 article in which Merton's account is written up has as its explicit aim the revelation of three ways empirical research (and the data thereby acquired) has a direct influence on theory-formation in sociology, in opposition to the common assumption that only theory affects theory (Merton, 1948, p.505).

[8] While Merton's example describes an impact on sociological theory, in other examples or in other fields the valued outcome of serendipity at the community level may be in the form of a new practice, new technology or new methods for producing knowledge.

examples of “breakthrough innovations” (de Rond, 2014, p. 10). Thus, his examples are all of serendipity with a valued outcome. Further, the capacity of the sagacious individual for making meaningful connections (that de Rond argues is the essence of serendipity) is more than acapacity for making connections. It also requires “creativity and practical judgment in matching observations of unforeseen events with findings reported by others, and in *selecting* which of these combinations might be *fruitful*” (de Rond, 2014, p. 10, emphasis mine). Finally, it is important to recall that the definition of serendipity offered by de Rond includes that the matching pairs identified by someone with the relevant capability be put to “practical or strategic use” (de Rond, 2014, p. 1). The value of the outcome of the connection determines whether the connection was sagaciously made, not just the capability for making the connection itself.

Friedel’s three-category account of serendipity also implicitly depends on the valued outcome as a third, necessary element. Again, the valued outcome gives the status of serendipity to the examples he draws upon. This is particularly clear in the example of Columbus’ discovery of the American continent. Columbus never admitted he had not landed in Asia, and so he never made a sagacious connection between his unexpected discovery (which he did not see as unexpected at all) and other knowledge to reveal the novelty of his find, its actual value, to himself. “But the result—the European knowledge of the New World—is still intimately associated with his efforts” (Friedel, 2001, p. 39). Thus, implicit in Friedel’s account is that the value of the outcome, at least as much as sagacity and chance, plays a role in identifying serendipitous discoveries.

Looked at in relation to chance and sagacity, we can see that the valued outcome is not only a feature of actual accounts of serendipity, but is necessarily a third element in the definition of serendipity. For one, none of the examples of serendipity recounted in the

literature would be told as narratives of serendipity if there hadn't been a valuable outcome. Serendipitous discoveries, that is, are necessarily discoveries, and discoveries are considered such (and not dismissed as incidental findings or mere accidents) because they are valued. As a consequence, an unexpected observation that led to a serendipitous discovery cannot be perceived as such until the discovery has been made. The valued outcome determines when an unexpected observation was serendipitous, in retrospect. Thus the category of serendipity itself can only be applied retrospectively, at the time or after a confluence of all three elements—chance, sagacity and a valued outcome—occurs. Finally, and as I will show in the coming sections, it is possible to have an unexpected observation recognized by a sagacious individual and not have a valued outcome. In such cases, neither is there serendipity; *viz.* there is no serendipity *without* a valued outcome.[9]

2.2 Tripartite Serendipity – From Individual Scientist to Scientific Community

Making the valued outcome explicit as a necessary, third element of serendipity also has the effect of highlighting the role of communities in serendipitous discovery. Accounts of serendipity that focus on chance and sagacity tend to also focus on an individual and her observation, and fail to pay sufficient attention to the process of discovery involved in serendipity in science. An exception is Merton, for whom the value of the serendipity pattern itself lay in the influence the outcome of that pattern has on theory-formation, and thereby on

[9] This counts for imagined cases of private serendipity as well, or serendipity to any degree. It doesn't have to be a highly valued outcome at the level of all society to be serendipity, it can also be a personal experience of chance, perceptive recognition and an outcome only you value. However, it is serendipitous discovery in science that interests me here, and not personal experiences. I would not argue that such experiences are impossible, but rather point out that they do not find a place in science so long as they remained private. If a discovery originates by accident, but no one tells that part of the story, it will not be known as serendipity; if a scientist makes a discovery that she does not share with anyone, it will not count among scientific discoveries as we know them.

the epistemic community of sociologists as a whole (Merton, 1948). Makri and Blandford, despite making the valued outcome explicit as an essential element in serendipity, focus their research on personal experiences of serendipity and thereby elide the importance of the community as a whole in enabling the serendipity process (Makri & Blandford, 2011).

Making the importance of the valued outcome explicit illustrates and provides an explanation for the importance of the organizational community to de Rond's account of serendipity. De Rond explicitly asserts that some of the breakthrough innovations in his examples could not have come about if those given credit for the discoveries had not had "the benefit of those around them," and that, "[s]erendipity, properly understood, also accentuates the importance of the historical and social features of the innovation process" (de Rond, 2014, p. 13). In his eagerness to isolate the essence of serendipity in a human capability, de Rond is left with various social aspects of serendipity that do not fit comfortably within his definition, and yet remain necessary to any accurate account of serendipity. In fact, in what seems an effort to accommodate the role of the community, de Rond suggests in the closing arguments of his article that the capability he describes may be a capability of organizations as well as individuals (de Rond, 2014, p. 14).[10] Rather than an argument for this idea, however, the reader is left with a series of questions about what kinds of organizational action could encourage or discourage innovations by way of serendipity.

Friedel's account includes consideration of the role of the community in determining when serendipity occurs, as well. For example, he claims: "A mere observation… does not constitute true serendipity" (Friedel, 2001, p. 43). The example Friedel describes at length, of

[10] This is not the only time de Rond is inconsistent in his approach to serendipity. He also says at the end that he has redefined serendipity as "the junction of a-causal but meaningful events" which is different than his definition of serendipity as a "human capability" but he does not remark on the slippage. De Rond does better work elsewhere, in a co-authored paper about the role of chance in strategic decision-making, but there the authors do not attempt to define serendipity (de Rond & Thietart, 2007).

the discovery of the fullerenes[11] in chemistry, includes details about publications, communications, networks, dispositions, and theories that, in addition to chance, "set the stage for serendipity" (Friedel, 2001, p. 42). According to Friedel, "true serendipity" is more than a single observation made wisely, but is rather a process that takes place within a community and can involve several people and many steps.

Thus, accounts of serendipity include the necessary third element, the valued outcome, in some way, and that valued outcome plays a logically necessary role in identifying when serendipity occurs. Further, because it is a community—the epistemic community of scientists, for example—that determines what value the outcome of chance and sagacity has, it is also a community that determines *when* serendipitous discovery occurs.

As suggested above, however, the status of the chance observation and the sagacity of the observer are dependent on the valued outcome; thus, it seems the valued outcome has a priority of importance in relation to the other two elements. This is not the case, however. Rather, all three elements interact to characterise one another and serendipity too. Sagacity is the element that drives the categorization of discoveries as serendipitous in science: if there were no wish to recognize the insight and actions of an observer, the discovery would not be described as serendipitous. Thus, the chance and valued outcomes are, in a sense, dependent on the sagacity element. Further, the chance element of serendipity constrains the kind of content that the valued outcome can have. An unexpected observation—one that is anomalous and surprising—is unexpected because prevailing knowledge is insufficient for explaining or

[11] I do not have the space to go into detail regarding the process of discovery of the fullerenes in chemistry. Friedel does a thorough job of describing that process of discovery, which takes place across institutions and over time as well as including multiple chance incidents. I refer the reader to his article for details (Friedel, 2001).

predicting the observation. Thus, the valued outcome of such an unexpected observation will, by definition, be novel in relation to prevailing knowledge or practice. All three elements are logically necessary, and each element plays a role in determining when a discovery is serendipitous.

To demonstrate the necessity and interaction of all three elements in serendipity, I now give a close description of each of the three elements, focusing on how they inter-relate. For each one, I note that paying attention to the community context—and not just to the individual observer and the observation itself—is key to understanding its role in serendipitous discovery.

2.2.a Chance

I have chosen to use the word "chance" to describe what is sometimes called the "accidents" element of serendipity, or what Merton captures with the descriptions "unanticipated" and "anomalous" in his account of the serendipity pattern. Chance is a more appropriate term to use because it captures the relationship between the unexpected observation, the observer, and the context in which serendipity occurs. That is, serendipity emerges unexpectedly from a context of ongoing processes. What is perceived to be by chance is in relation to those processes:

> …chance must […be] grounded in features of the process that can produce the outcome: … [e.g.: a] coin-tossing trial, including the mass distribution of the coin and the details of how it is tossed … plus the background conditions and laws that govern the trial. Whether or not an event happens by chance is a feature of the process that produced it, not the event itself. (Eagle, 2012)[12]

[12] http://plato.stanford.edu/entries/chance-randomness/. Accessed 18 July 2015.

What is perceived as chance, given this definition, is whatever occurs unexpectedly in respect to the processes underway.

Serendipitous discoveries frequently originate while a researcher is actively engaged in a project unrelated to the valued outcome. For instance, Viagra, the now famous drug for erectile dysfunction, was found to have this use during a clinical trial testing the chemical compound for its potential as a cardiovascular drug. When researchers had trouble retrieving leftover samples, they inquired as to why participants wanted to keep them, and uncovered an unanticipated side effect that they profitably exploited for its therapeutic potential (de Rond, 2014, p. 7). In this case and in others, the people who experienced serendipity were already on the hunt for something else when it arose—when by chance they were presented with a new, valuable direction for further investigation. Philosopher of science Aharon Kantorovich chooses serendipity to describe the injection of novelty into the progress of science precisely because it represents for him such a change in research direction or, in some cases, the emergence of a wholly new research program out of the programs already underway (Kantorovich, 1993, p. 154). Merton describes the datum in his example as having "conducted [the researcher] along an unpremedi[t]ated by-path which led to a fresh hypothesis" (Merton, 1948, p. 509). In many of the examples of serendipity in science, scientists who are engaged in normal scientific activity toward a particular end make unexpected observations that take their research in new directions.

However, other cases of serendipity—including the example of Fleming's discovery of penicillin, mentioned in virtually every account of serendipity—are not so clearly distractions from intended paths. Fleming's encounter with the mould that would later be refined and developed into the lifesaving antibiotic was by chance. He had left petri dishes that had been used to cultivate bacteria unwashed while on vacation and the famous mould had landed and

propagated in one of them while he was gone. Upon his return, Fleming observed that the mould had affected the dish's other contents. Having just come back from vacation, Fleming did not make this observation while explicitly engaged in a search for something else, but his observation was indeed unexpected. [13, 14] The specific relationship between what someone is doing at the time and serendipity varies between examples. Serendipity does not always occur when someone is actively looking for something else, but it does always occur unexpectedly.

Further, serendipity is not only unexpected from the perspective of the person making the observation and the processes underway, it is also unexpected from the perspective of an epistemic community. As noted above, the observation may have arisen by chance in relation to the activity already ongoing in that context, but it was also by chance observed by a person sagacious enough to recognize its potential value. The value of such an observation to science, however, remains potential unless the community of scientists also takes it up and accepts it into the body of scientific knowledge. Thus, the observation must either be made or promoted within a community that will take it up.

For example, Friedel suggests that Galileo's revolutionary observation of the moons of Jupiter was serendipity because he did not expect to find something of such value when he looked to the stars with his new tool, the telescope (Friedel, 2001, p. 40). The importance of Galileo's observation was that it called into question the same "zeitgeist" (Simonton, 2004) that caused Copernicus to hold off on publishing his heliocentric depiction of the cosmos: Ptolemaic geocentrism was the official doctrine of the time. Galileo's consequent troubles with

[13] Kantorovich uses Fleming, mistakenly, as an example of a scientist who was engaged in experimentation when his unexpected observation was made (Kantorovich, 1993, p. 169).
[14] There are further questions to be raised of this example, such as whether Fleming was actually thinking about and looking for antibiotic effects in general, at the time he made his observation of the contaminated petri dish. These are left to the detailed discussion of Fleming and penicillin in Chapter 3.

contemporary authorities in the church are well-rehearsed in histories of science. The importance of having a receptive community for one's ideas was not lost on Copernicus when he withheld his own publication, and was infamously dismissed by Galileo.

Chance, therefore, describes not only the context in which an unexpected observation is made at the level of the individual, but also the context in which a serendipitous discovery is made, at the level of the community. Kantorovich makes the following claim: "Discoveries are not made in a social vacuum. The discovery is "in the air," or "the time is ripe" for it. This means that (a) the state of knowledge in the scientific community is ready for *generating* the discovery and/or (b) the time is ripe for the *acceptance* of the new idea or theory" (Kantorovich, 1993, p. 189). Not only does the epistemic community need to be ready for one of its members to recognize the value of an unexpected observation, it must also be ready to take up that observation into a process of discovery. The fact that one particular observation, made by one particular person,[15] in the right community and at the right time is what gives rise to serendipity attests to the role that chance plays throughout the process of serendipitous discovery.

Finally, the observation is unexpected because it is, as Merton suggests, anomalous and surprising: the observer and her community could not predict it would occur and cannot explain it away when it does. Thus, serendipity introduces novelty insofar as it extends or modifies theory or practice by introducing new and surprising knowledge to an epistemic community.[16]

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[15] It has already been mentioned that it takes a sagacious observer to note the potential value of an unexpected observation, and further that other observers would not have noted the same thing about that observation, but also consider the fact that many observations significant to science—such as Newton's observation that objects fall as a result of the effects of gravity—do not represent the first time that same observation was made by a human or even a scientist.

[16] This does not mean that all serendipity is revolutionary or that the change it initiates is always radical, but what inspires the curiosity of an observer is the novelty of the potential value the observation represents. If the observation were further proof of a theory already familiar, for example, then it would not be unexpected by the researcher, who could explain its occurrence at the time. Serendipity does sometimes solve a *problem* that is already familiar, but in a surprising and unanticipated (unexpected)

2.2.b Sagacity

The concept of sagacity is both epistemologically interesting and complex. Unfortunately, its current treatment in the literature is difficult to parse. In this section, I begin with a quick review of the literature to show that approaches to sagacity narrow to two aspects. The literature provides several approaches to sagacity. Sagacity is depicted as an expression of personal characteristics and behaviours, as the product of a prepared mind, and as a particular epistemic skill. It is, however, at base a category of appraisal. It reflects an evaluation of two aspects of a person's role in serendipitous discovery. First, describing someone as sagacious praises both her insight and actions when she takes advantage of an opportunity given by chance. As well, sagacity signifies an evaluation of the agency of that individual within an epistemic community. I will argue that epistemic agency is the appropriate lens for understanding how sagacity can be about epistemic insight and action, and also about appraisal.

The sagacity of people credited with serendipity is often described in the serendipity literature as the product of personal characteristics or behaviours of those people, similar to the kinds of characteristics and behaviours often attributed to creative people. Merton and Barber suggest the following lists of character traits associated with serendipity: "alertness, flexibility, courage, and assiduity," and "curiosity, spontaneity, imaginativeness, a sense of adventure." (Merton & Barber, 2004, p. 226) In his review of serendipity in science, Royston Roberts concludes that sagacity boils down to two such characteristics, curiosity and perception (Roberts, 1989, p. 224). Walter Cannon suggests in his autobiography that serendipity comes most to those "whose researches range extensively." (Cannon, 1945, pp. 73–74) The microbiologist Salvador Luria argued that a "controlled sloppiness" was the hallmark of great

way. Thus, the "new and surprising knowledge" serendipity introduces may be a new method, new technology or a new practice—see the section on valued outcome below.

discoverers, who keep old problems hanging about to clutter their current research (quoted in Merton & Barber, 2004, p. 193). However, these characteristics and behaviours associated with creativity—such as sloppiness, imagination and wide-ranging interests—are often meant to explain the increased likelihood for some *individuals* to make unexpected yet potentially valuable observations.[17] These personal characteristics of individuals do not help to identify when a discovery is serendipitous.

On the other hand, sagacity is as frequently related to intellectual training and skill—that most famous characteristic noted by Pasteur and often quoted, the "prepared mind" that "chance favours." As Stevan Harnad interprets, Pasteur is referring to the need for one to "even be in a position to recognize something worthwhile and original for what it really [is]" (Harnad, 2006, p. 164). Merton (1948) gives primary importance to the prepared mind in his account of serendipity when he claims that "The more [the investigator] is steeped in the data, the greater the likelihood that he will hit upon a fruitful direction of inquiry," (p. 506) and "[serendipity] obviously requires a theoretically sensitized observer" (p. 507).

It may seem that training and experience would promote orthodoxy and thereby increase the chances a researcher will toss out an unusual result, missing an opportunity for serendipity (e.g., see Meyers, 2007). However, the experienced researcher is often more likely than the nervous novice to recognise the potential significance of such outlier observations

[17] Qualities like these, related to the creativity and self-direction of a researcher, are often looked for as reasons why some individuals may be more 'serendipitous' than others. Such individuals are sometimes called 'serendipitists'--a title invented by Joyce for use in his anti-etymological work, *Finnegan's Wake* and used by several authors in the serendipity literature, meant to indicate those individuals who make serendipity happen. As I have pointed out already in this Chapter, no single individual in science is likely to be capable of making a change to accepted theory alone, and therefore calling any particular individual 'serendipitous' or a 'serendipitist' begs the question I am trying to answer, by suggesting that such an individual indeed carries the weight of making serendipity happen (and, correspondingly, that the key features of serendipity will be features of that individual).

(Merton & Barber, 2004). Further, experts and those with epistemic authority in their community have a greater chance of being able to (or of enabling someone else to) follow through and complete a process of serendipitous discovery than novices or outsiders may. Thus the agency of an individual within a community, rather than features about that individual herself, determine whether she will express her sagacity by enabling a serendipitous discovery.

When described in terms of creativity or intellectual skill, sagacity is seen as making a connection of some kind, between what is already known (either what the sagacious individual already knows or what is available to her as knowledge) and an unexpected observation. Merton suggests that it takes a particular skill, "to detect the universal in the particular" (Merton, 1948, p. 507). The relevant skill has also been described as abduction[18] (van Andel, 1994), making meaningful connections (de Rond, 2014), and bisociation (Cunha, Clegg, & Mendonça, 2010), among other terms related to analogical reasoning, problem-solving and perception (Merton & Barber, 2004). However, examination of examples of serendipity from the literature shows that making the relevant connection can involve several people across disciplines, communities and locations. If sagacity is an intellectual skill exercised by an individual, it is not only that.

Consider the serendipitous discovery of background cosmic radiation, evidence for the big bang hypothesis about the origin of our universe. Astronomers Arno Penzias and Robert Wilson were trying to eliminate noise from their radio receiver, to no avail, when it occurred to them the noise may not be caused by a source on or near their receiver, or even within our

[18] This is a form of reasoning described by Charles Peirce. What abduction is, and how it fits into the reasoning processes involved in scientific discovery, is a matter of debate and, although it is very interesting, it is too large an issue to take on for my purposes here. If the reader is interested in pursuing this avenue, there are several sources with which she can begin (Hintikka, 1989; McKaughan, 2008; Paavola, 2004; van Andel & Bourcier, 2001).

galaxy.[19] Later, when they encountered proponents of the big bang theory from Princeton University, they realized their noise may be the microwave radiation the Princeton team was hoping to find.[20] Thus, while they were able to detect that the noise may be significant, they did not at that time know what the noise's ultimate value might be. The knowledge they needed to make the relevant connection was available to them, but not known by them at the time they made their unexpected observation. The serendipity of that observation, however, and indeed the sagacity of Penzias and Wilson were both ultimately dependent on the availability of that knowledge.

In other words, beginning with the assumption that sagacity is a characteristic of an individual would be begging the question in what sagacity consists of. Rather, my literature review shows that sagacity is typically used in two ways, often conflated—both the epistemic agency of the individual, and the actual outcome of her insight and actions are considered signs of her sagacity. First, calling someone sagacious is a reflection of that person's epistemic agency in the community: labelling the discovery a person has enabled "serendipitous" has the effect of recognizing that person as a contributing epistemic agent in the community. Second, in order to enable a serendipitous discovery, a person must express her sagacity through her insight and actions. The outcome of those insight and actions—if it is valued by a community—determines whether the person responsible for them will be recognized for her sagacity.

In order for a discovery process to be taken up by the relevant community, the researcher who recognizes the significance of an unexpected observation must do some work

[19] Famously, they imagined and put considerable effort into eliminating the possibility that it was bird guano causing the noise.

[20] The story of this discovery is readily found in collections of serendipity and online. For example, refer to this summary and other sources related to their winning of the Nobel Prize for their discovery: http://www.nobelprize.org/nobel_prizes/physics/laureates/1978/speedread.html. Accessed 20 June 2015.

(epistemic activity) to enable that significance to be confirmed and accepted by the community as knowledge. De Rond suggests that "human agency" is the proper focus of analyses of serendipity; he means to call attention to the fact that it is human action that makes serendipity come about, and not principally chance. But this role for human action extends beyond a person's intellectual capability for making the meaningful connection that is de Rond's focus. The capability, when exercised, must lead to a change at the level of the community—in theory or practice, so long as it is of value to that community.

Further, as Merton's serendipity pattern suggests, it is not only the unexpectedly observed datum that leads to a discovery but rather the fact that it inspires curiosity in an appropriately strategic researcher who then does needed work to make serendipity happen. Merton is explicit about the fact that in order to make sense of the observed datum—"to fit it into a broader frame of knowledge"—the researcher takes actions such as "exploring further" and making "fresh observations" (Merton, 1948, p. 506). Action needs to be taken in addition to recognizing the significance of an unexpected observation—the researcher needs to take steps to get from an observation to a discovery. The human agency de Rond sees behind serendipitous discovery consists not only in perceiving a connection, but also in the actions perceivers take and the agency perceivers have within their epistemic communities.

Whether a researcher is judged to be sagacious is also dependent on factors about the social-epistemological context in which the discovery process is completed. An epistemic community judges a person to be wise in response to her contributions of knowledge to that community. The unexpected observation made and duly noted by the researcher must actually be recognized by the community as a contribution of knowledge, for example, for her to earn the status of a sagacious individual from that community. Taking up a researcher's observation and changing accepted theory or practice, the requirements for being judged sagacious, are

dependent on a community's assessment of the value of that observation. Thus, judgments of a researcher's sagacity take place within the social-epistemological context created by that community.

In sum, the researcher must be recognized by her epistemic community as having produced knowledge. For this to happen, her methods and/or her expertise must be recognized as being (normally) capable of knowledge production.[21] Applying the category of serendipity to a discovery includes the implicit recognition of the researcher who made the relevant unexpected observation as a trusted *epistemic agent*.

I employ a conception of epistemic agency derived from Cynthia Townley's work in feminist epistemology of ignorance. Townley understands epistemic agents to be "interacting members of epistemic communities" (Townley, 2011, p. 7). In turn, "an epistemic community is a network of relationships between agents engaged in epistemic activities and practices..."[22] (Townley, 2011, p. 2). Scientific communities are examples of epistemic communities. Further, as Townley argues, "full membership of an epistemic community includes having the connections to other agents that enable (but also sometimes restrict) my epistemic agency" (Townley, 2011, p. 2). Agents within an epistemic community are interdependent, not just socially or politically but also epistemically.

Further, epistemic agents that contribute to the community do not always do so straightforwardly as knowledge-providers, but sometimes as mentors or exemplars of epistemic

[21] This does indeed effectively eliminate the consideration of private serendipity; see footnote 11.
[22] The rest of this quotation reads: "[such as] acquisition, distribution and sharing of knowledge, including investigation, education, archiving, informing, learning and reflecting upon these activities" (Townley, 2011, p. 2).

virtues, including "those that encourage other members of the community to do well with knowledge."[23] Doing "well with knowledge," consists in being a good epistemic community member overall. As Townley suggests, "Being trusted and treated as credible is good for me as an epistemic agent, although it does not always mean that I know any more" (Townley, 2011, p. 13).

Important to Townley's explication of the relationship between agents in a community is the idea that an agent must be recognized by others in order to do much epistemic work. "A mature epistemic agent has the competence to engage with other agents and can recognize and be recognized by them as an epistemic agent" (Townley, 2011, p. 3). Sagacity is related to this kind of epistemic trust. Serendipity is a category of appraisal, signifying a community's recognition that someone is a credible epistemic agent, generally for reasons that lie beyond the demonstration of her sagacity in a particular case.

Factors that are relevant to the garnering of appraisal through recognition of sagacity in serendipity are related to the community. A community's trust in her insight about the potential value of an unexpected observation reflects the agent's role within that community and the corresponding agency she has within that community as a (potential) knowledge-producer. Epistemic communities, interactive communities of interdependent knowers and knowledge-producers, and specifically scientific epistemic communities, determine what data will be seen as evidence for a hypothesis that results in a valued discovery (Longino, 1979). Patterns of authority, standard methods, and other constraints on what kinds of knowledge can be discovered, how and by whom, are both social and epistemological.

[23] For example: "not just to collect or acquire [knowledge], but to engage authoritatively with others, to seek appropriate others on whom to depend, to trust and defer wisely, to consult in order to calibrate one's own standards, to assist others to maintain appropriate standards (directly or indirectly, for example, by cultivating systems that reduce bias or enhance inclusiveness), and so on" (Townley, 2011, p. 8).

Sagacity itself is not a wisdom concerned only with the epistemological significance of an unexpected observation. Rather, it requires the two-part inference that (1) the observation is significant, even though unexpected in relation to her research at that time, and (2) it is significant in relation to the epistemic community (e.g., of scientists) and the current state of its knowledge. More than making a connection between an unexpected observation and current knowledge, sagacity also consists in *knowing when and how such a connection is likely to lead to a discovery*. Following Simonton, both the ability to make a connection and having the knowledge needed to see the value in such a connection are dependent on opportunities (e.g., for skill development, communication of ideas, and both gaining and demonstrating experience) that are given in part by one's agency within a community.[24] So too is the epistemic agency required for bringing that connection to fruition as a discovery.

Whereas chance is generally not considered a legitimate method for producing knowledge, the inclusion of sagacity explains how a chance event can result in a (justified) change in theory. One implication of this is that the category of serendipity has a normative valence. In communities where it is disreputable to be associated with lucky discovery, researchers are unlikely to claim their contributions were serendipitous. Similarly, novice researchers who have yet to establish reputations as knowledge producers are less likely to risk testing community acceptance by declaring themselves to have benefitted from a chance observation, lest they be deemed merely lucky. Thus, an observer who seeks to be recognized for her role in serendipity must also take into account the conditions by which insight and actions are recognized as signs of sagacity. A researcher who completes (or enables others to

[24] This is not to say that the social world is chaotic or random, but rather that people do not have full control over their destiny. See Malcolm Gladwell's book, "Outliers", for example. This volume is a series of stories of success that seem to be due to the perseverance or characteristics of the individuals involved, but actually can be traced to contingencies such as culture, class, or date of birth.

complete) a process of serendipitous discovery and is recognized for doing so has acted in the right way to attain this recognition, in accordance with her context and the agency she has within her community. If a researcher has earned the label of sagacious because of her involvement in serendipity, it is because she not only recognized the strategic nature of the unexpected observation, but also strategically communicated it, stored it, or put it to use—making it accessible to other community members.

In conclusion, while the sagacity involved in serendipity is understood in a variety of ways throughout the literature, it can be seen as a more unified concept through the lens of epistemic agency. Epistemic agency is required to have the insight and to complete the work to enable an unexpected observation to be taken up by a community into a process of discovery. Further, categorizing a discovery as serendipitous is recognizing and appraising the epistemic agency of those involved in making an unexpected observation and thereby contributing to that process of discovery.

2.2.c Valued Outcome

The outcome in every example of serendipity is valued by someone.[25] Makri and Blandford make the valued outcome explicit as a necessary element in serendipity by conceiving of serendipity as a process. The personal experiences of the researchers they interviewed, alongside a literature review, confirmed their belief that the valued outcome ought to be a part of their account of the serendipity process. They explain the valued outcome as expressed by some of their research participants as follows:

[25] In fact, an accident that leads to an undesired outcome is not serendipity but a mistake, an error or simply an accident—in these cases people are deemed *un*lucky. It is also possible that no outcome results from the efforts of a researcher to follow up on an unexpected observation she considered potentially valuable. In such cases a negative valence will still apply: such a researcher has wasted valuable time and resources, possibly, and may be seen as "stupid" as a result of her convictions. None of these are cases of serendipity. (Thanks to Françoise Baylis for pointing this out.)

> It was also proposed that there must be a **clear, positive outcome** in order for an event to be classed as serendipitous. This might involve there being a change in a person's state of knowledge or awareness as a result of the event (i.e., a *change in the head*) and possibly, although by no means always, a change in the physical environment (a *change in the world*), where the world might be slightly different as a result of the serendipitous event than it would have been had it not happened. (Makri & Blandford, 2011, p. 5, emphases theirs)

Makri and Bandford take as their focus the personal experiences of serendipity shared by the academic researchers who are their research participants. Their conclusions are guided by the reflections of those participants on patterns in those shared experiences (Makri & Blandford, 2011, 2012a, 2012b). Thus, the valued outcome, in their account, may be a change in perception ("a change in the head") and so valued only by that individual person. As Makri and Blandford observe, serendipity is a category applied only in hindsight to a process that is already or practically complete (Makri & Blandford, 2012a, p. 3). The processes in their examples, drawn from personal experiences and not the history of science, are begun and completed by the same people who value their outcomes. In some cases, the process begins and ends in the same moment—for example, when the serendipitous discovery is of an article that proves highly valuable for one participant's master's thesis research (Makri & Blandford, 2012a, p. 12).

In contrast, many of the serendipitous discoveries I discuss are particularly valuable, not just to the scientific community but to society as a whole—the medical discoveries of penicillin, antibiotic treatments for ulcers and the possible discovery of a therapeutic option for sufferers of Alzheimer's disease, have and perhaps would merit a Nobel Prize. The tripartite account of serendipity applies to all cases of serendipity, whether the relevant community is large or small, and regardless of the degree of (positive) value that the community assigns to the outcome. The

relevant community is whatever community is comprised of the people who value the serendipitous discovery at hand. I focus in this dissertation on serendipitous, *scientific* discovery in medicine; the relevant community is therefore a scientific and medical community.

Valued outcomes of serendipity in science and medicine are not limited in terms of the kind of discovery being made, so long as those outcomes are both unexpected and yet valued by the scientific and medical communities. A serendipitous discovery in science may have an epistemic outcome that extends or modifies theory (Galileo's observation of the moons of Jupiter), may be a technological innovation (antidepressant drugs), or may introduce a new and successful methodology (Kepler's laws). As in Merton's example of the sociological researcher above, the value of the outcome of serendipity to the relevant community is what confirms (and gives content to) the value of the chance observation as well as the sagacity of the observer.

2.2.d The Community

There is empirical evidence that serendipity in science and medicine is not individualistic, but is rather an activity requiring the cooperation and interaction of several people. Abigail McBirnie did extensive research to quantify the way in which serendipity in science occurs, drawing from narratives written by scientists. These scientists reflect on their past discoveries that led to the publication of some of the most-cited articles in the history of science. McBirnie argues from her results that the category of serendipity does not describe one individual's experience, but rather is "concerned with individuals in relations" (McBirnie, 2012, pp. 2, 61–62). By looking at relationships between individuals and/or processes, she is able to assess that the average number of participants involved in the serendipitous discoveries she examines is fifteen or sixteen, and the average number of processes engaged is between 31 and 33. Further, a minimum of two different times and/or locations were

involved in each of the incidents of serendipity she assessed (McBirnie, 2012, p. 336). It takes a community to bring about a valued outcome and to complete a process of scientific, serendipitous discovery.

As well, it may be that the scientist who perceives the potential value of an unexpected observation is quite different from the scientist or even epistemic community who completes the discovery process. A process of serendipitous discovery may extend (far) beyond the time, place, community or researchers involved in the original observation. Simonton (2004) points out that even when all necessary conditions for a discovery have been met, there may be chance or contextual factors that prevent a discovery from being made by that person or in that moment: "As a consequence, many discoveries consist of ideas that have been in existence for decades, if not centuries" (p.92). One individual may perceive the observation as potentially significant, while a different person perceives that significance in relation to theory accepted by the (different) epistemic community. In particular, in processes of scientific discovery, "[s]ometimes the scientist who makes the [observation] is not aware of the full significance of the discovery while other scientists complete the task" (Kantorovich, 1993, p. 154).[26] Thus, the person(s) who bring about the valued outcome of an unexpected observation may not be the same as she who made the unexpected observation.

In sum, explaining serendipity entails looking further than the sagacity of a single individual or the immediate context of an unexpected observation, toward the broader social-

[26] Kantorovich uses the word "discovery" in this quotation rather than "observation." His meaning of discovery in this instance is closer to my term "observation" as it is being used in this dissertation, and does not match well with the term "discovery" as I am using it. To avoid confusion, I made the switch.

epistemological context in which the discovery as a whole[27] takes place. That is, it entails looking at the relationships between researchers as well as the values and norms of their communities. Not only the insight and actions of an individual, or the unexpectedness of an observation, but also the context in which a serendipitous discovery occurs determine whether that discovery will be made, and by whom. In the case of scientific or medical serendipitous discovery, that context is the greater scientific or medical community.

2.3 Implications of Retrospectivity

The three elements of serendipity come together within a social-epistemological context. Their confluence is contingent on the relationship between a chance observation, the epistemic agency of its observer, and the values as well as the current state of knowledge of the epistemic community. The identification of serendipity, because it depends on the valued outcome being determined, is retrospective. That serendipity is retrospectively identifiable is further reinforced by the fact that it is typically expressed in narrative form: narratives of serendipitous discovery express recognition that chance, sagacity and a valued outcome have come together in a single discovery process.

However, not all chance events will be regarded by an epistemic community as a legitimate source of knowledge; not all agents who otherwise have met the conditions for sagacity will have their observations and insight taken up by their community; not all potentially valuable outcomes will be valued immediately or at all. What counts as serendipity, and what gets included in a narrative of serendipitous discovery, is just as contingent on communities as on the confluence of the three elements. I show how this plays out in two paradigm examples of serendipity, described in detail in the next chapter.

[27] Note that the discovery process—from observation to outcome—need not be thought of as linear, but could just as well be iterative, lateral, and interactive with other discovery processes.

Chapter 3 – Paradigms of Serendipity

Examples of serendipity in the literature are generally anecdotal accounts or recollections of events from history that contributed in some way to valued discoveries in science. These retrospective narratives of serendipity provide hindsight into what kinds of epistemic agents and what kinds of epistemic actions led to serendipitous discoveries. The narrative form lends a sense of necessity to the events and individuals included in the retelling of a process of discovery. However, it is not of necessity but rather contingently that particular events and individuals come together in a process of serendipitous discovery. Further, unlike a narrative, discovery is not necessarily a linear process from origin to outcome, but could be dynamic, iterative and move laterally across communities. A discovery may have happened in a different way than it did, or those events and individuals may have failed to or have been prevented from contributing to that process of discovery. Consequently, contingencies may be inaccurately presented as necessities in accounts of serendipity that use retrospective narratives to delineate necessary and sufficient conditions for serendipity. The tripartite account outlined in the previous chapter offers an alternative—more robust—analysis of narratives of serendipitous discovery that avoids imposing such assumptions about how discoveries are made.

To demonstrate that serendipity is best defined under the tripartite account—as a concept including chance, sagacity and a valued outcome—I now examine two paradigmatic cases of serendipity. The first is the story of Barry Marshall, a novice gastroenterologist who is credited with having insight into the potential value of the observation that *H. pylori* bacteria were found in the stomachs of humans. Marshall is also known for having gone on to confirm and popularize the conclusion that these bacteria caused stomach ulcers, an idea contrary to prevailing medical opinion at the time. The second is the story of Alexander Fleming's

observation of his famous petri dish and the series of events initiated by that observation that led to the discovery of penicillin. Both narratives include an unexpected observation, both stories include accounts of the sagacity of their protagonists, and both conclude with a valued discovery in medicine.

Using the tools provided by the tripartite account of serendipitous discovery, I show that the stories of Marshall and of Fleming differ in an important way. Whereas Marshall plays the role of protagonist throughout the discovery narrative, Fleming's active role basically ends before penicillin is discovered. This difference allows me to highlight the importance of the valued outcome as a third element and how social and epistemological factors about the scientific (and broader) community can determine what counts as serendipitous discovery in science.

3.1 Barry Marshall and the Discovery of *H. pylori*

Barry Marshall was awarded the Nobel Prize with Robin Warren in 2005, for their discovery of *Helicobacter (H.) pylori,* a bacterium now associated with and thought to cause some stomach ulcers. Before this discovery, gastroenterology doctrine was that the stomach was too acidic an environment for bacteria to grow, stomach ulcers were caused by stress, and these ulcers were best treated by reducing the acidity of the stomach with medicine and reducing the stress with therapy.

In 1981, while in training in cardiology, Marshall was assigned to work with pathologist Robin Warren. Warren had recently observed unfamiliar, curved bacteria in the stomachs of several clinic patients. These patients needed to be followed up and, if clinical illness presented, diagnosed. One of the patients happened to have been seen by Marshall before, who at that

time had been unable to successfully diagnose her stomach pains. While Marshall's initial chart review of these patients revealed no obvious relationship between diagnoses and the bacteria, he was sufficiently interested in that possibility to continue researching. Reflecting upon the interest he took in Warren's findings, Marshall says, "I could see an interesting paper being produced, perhaps in an obscure microbiological journal, but had no idea at the time of what we were really about to discover."[29]

In 1982, Marshall designed a study involving 100 participants (to make percentage calculations of the results easier to do) to "determine the prevalence of the bacteria in an endoscopy population, to try to culture the organism, to see what diseases were associated with it and to detect an infection source if there was one" (Marshall, 2006). The study confirmed 100 percent correspondence between the presence of the bacteria and a diagnosis of duodenal ulcer (Marshall, 2006, p.257). At the same time, Marshall conducted a literature search and learned that spiral bacteria had been found in human stomachs on several occasions and yet had been consistently assumed to be incidental.

As the story goes, the initial attempts by Marshall and Warren to publicize the observation were unsuccessful. Their first publication on the matter was in the reputable *Lancet*, but was published as two separate letters rather than a report on experimental results. The letters suggested that ulcers may be caused by bacteria; this idea was regarded as "preposterous" by members of the gastroenterology community and rejected by the Australian Gastroenterology Society. Further, Marshall was called a "madman," and his claim that bacteria may even cause stomach cancer was dismissed as "crazy" by leaders in the scientific and medical community (Thagard, 1998a, p. 121). Marshall nevertheless pursued his idea, to the

[29] Quoted from 'Barry J. Marshall – Biographical' posted on Nobelprize.org, accessed 30 May 2015, [http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/marshall-bio.html].

point where he conducted an experiment on himself, swallowing a pure culture of the bacteria to give himself gastritis, thereby showing that the bacteria could cause illnesses of the stomach.[30] In a 1999 editorial essay in the *New York Times*, Alice Dreger writes:

> Consider the case of Dr. Barry J. Marshall, the young Australian physician who discovered that peptic ulcers are caused by a bacterium, Helicobacter pylori. Dr. Marshall's colleagues, stuck firmly in the received wisdom that ulcers are caused by psychological stress, thought his idea absurd. They ignored for years the evidence for a bacterial cause for ulcers—evidence Dr. Marshall was able to see. So convinced was Dr. Marshall that he was right, he used himself as a guinea pig, drinking the bacteria to prove that it turned his once-healthy stomach diseased. Passionate? Yes. Passionate enough to push until his colleagues finally recognized the truth of his ideas. (Dreger, 1999)

3.1.a *H. pylori* as a Serendipitous Discovery

The observation of *H. pylori*, and the consequent discovery of its relationship to stomach ulcers, was unexpected. Marshall did not immediately recognize its strategic importance, but in following up on the observation he came to see it as a possible correction to what, in light of this discovery, were inaccurate assumptions and practices in gastroenterology.

Paul Thagard (1998a) argues that the original observation and early research Marshall did to confirm that the spiral bacteria Warren had found was a new species, the habitat of which is the human stomach, "is best described as the result of serendipity and surprise" (p. 115). In terms of the process of discovery that is my focus—the discovery for which Marshall and Warren were awarded the Nobel Prize—the value of this new species was not purely epistemic,

[30] Note, he did not thereby show a direct correlation between ulcers and the bacteria, as his own case of gastritis cleared up on its own whereas ulcers are a long-term condition that require treatment.

but is retrospectively valued because of its impact on the theory and practice of gastroenterology. The clinically valuable discovery is that some (peptic) ulcers can be treated with antibiotics. This outcome is a result of Warren's unexpected data and Marshall's insight into its potential significance and epistemic work. While Thagard does categorize the first steps of this discovery process as serendipity, he departs from my tripartite approach insofar as he separates the overall discovery process into three different "discoveries." However, the value of discovering *H. pylori*, and the reason Marshall and Warren shared the Nobel Prize, is found in the ultimate outcome that is the (serendipitous) discovery that ulcers can be treated with antibiotics. It is this valued outcome that completes the process begun with the unexpected observation of the unfamiliar bacteria followed up with sagacity by Marshall.

Two features of the observation of *H. pylori* and the research that confirmed its existence show that *H. pylori* was an unexpected observation. First, Warren was not looking for bacteria in the stomach when he found it, and Marshall was not looking for a new discovery in gastroenterology when he took on his project (Thagard, 1998a, p. 115). Second, successful cultivation of the bacteria for study was the result of chance. The first plates were discarded before a culture could grow, because of a hospital policy at the time related to an outbreak of a "superbug" in Western Australia. The desired results were finally obtained because the staff were away on Easter vacation, and so the plates were allowed to cultivate for five days, giving enough time for the bacteria to grow (Marshall, 2006). Marshall followed up on the observation of this bacteria with an extensive literature search, confirming that it had not been previously named or investigated. This step in the discovery process thus consisted in demonstrating the existence of a previously unidentified species of bacteria present in the stomachs of humans.

The value of this first step in the process was not apparent, however, until the discovery process was complete. As such, while the first step in the discovery process is properly described

as serendipity, completion of the discovery process is needed to justify that description. The observation of a new bacterium was not just an interesting and unexpected observation, but the first step in a discovery process that had a valued outcome for medicine and that can be traced, retrospectively, to that unexpected observation.

3.1.b Marshall's Sagacity

The passage from Dreger's essay quoted above highlights the two aspects of Marshall's wisdom that led to his playing the role he did in this discovery narrative. First, Marshall was able to see something that others had failed to see, namely that bacteria were prevalent in human stomachs and, subsequently, that they occurred frequently in stomachs that suffered from ulcers. Further, he saw this observation as significant—he saw it may have strategic significance in relation to prevailing theory about ulcers and, more importantly, about the best way to treat them. For this reason, he followed up on the observations made by Warren, which brings us to the second aspect of Marshall's wisdom: he was convinced about the significance of Warren's observations, and he became passionate about convincing others of the same. In the narratives told of Marshall's discovery, such as Dreger's brief recounting above, there is considerable overlap between his insight and his passion.

By Marshall's own reckoning, he was initially uncertain about the nature of the significance of the bacteria that Warren had been observing in patient stomachs (Marshall, 2006). Warren needed someone to diagnose the patients before he could draw any correlations; Marshall designed a study to observe those correlations, without prejudice about which diseases were likely to be present when the bacterium was present. He recognized that the spiral bacteria could be a significant discovery for medicine, but did not yet know what the outcome of that discovery process would be. The work he did to find correlations through

comparative studies, the thorough review of the literature he undertook, and the experiment he conducted on himself together enabled the discovery that would later earn him the Nobel Prize: the "discovery of the bacterium Helicobacter pylori *and* its role in gastritis and peptic ulcer disease."[31] The original observation, or the "datum" in Merton's terms, was the presence of bacteria in the stomachs of humans. Following up on that observation, Marshall did the work to show how the datum is strategic: his epistemic work took an unexpected observation of the presence of a spiral bacterium in stomachs and applied it to theory, suggesting that the presence of this bacterium was not incidental but rather revealed a causal relationship with known stomach ailments. The valued discovery was not only that this is true, but that, consequently, many ulcers could be cured with antibiotics, potentially usurping the common practice of treating ulcers in perpetuity with antacids.

3.1.c The Narrative of Discovery

Focusing on Marshall's passion as the catalyst for making the discovery that ulcers might be cured with antibiotics presents a linear, progressive story of a discovery that was caused by the insight and actions of a single individual. Such an approach suggests that this discovery could not have occurred without the involvement of Marshall, whose sagacity allowed him to see the significance of Warren's original observations and whose perseverance brought that observation to fruition as a discovery. However, as Marshall's literature review revealed, others had observed the spiral bacteria as well, and it is possible that some other researcher could have pursued the discovery if Marshall had not. As well, the discovery could have occurred during routine experiments, under different circumstances, and thereby not have been a serendipitous discovery—it is possible that after years of using antacids to no avail, gastroenterologists

[31] Quoted from Nobelprize.org.

themselves would have pursued a different approach to ulcers. So, while the unexpected observation and the sagacity of Marshall are necessary elements of the narrative of serendipitous discovery that is constructed out of the events that actually occurred, their confluence with a valued outcome was also dependent on factors beyond Marshall, his observation and his sagacity.

Further, the insight of Marshall, even if we include the wisdom expressed in his perseverance of the discovery, was not sufficient for turning this unexpected observation into a valued outcome. He also needed to have and to exercise epistemic agency, which is dependent on the values and perceptions of one's epistemic community. In Marshall's case, what enabled the acceptance of his claims and the results of his clinical research by the gastroenterology community was his collaboration with a network of researchers in the broader scientific community. As Thagard points out, this collaboration was necessary to the discovery of *H. pylori*'s relationship to ulcers. For example, Marshall and Warren needed the expertise of others during their research, to take and to analyse biopsies and to identify cases of gastritis as well as other jobs necessary to acquire and compare the data from clinical research. The published report on their first study thanked more than a dozen people for their assistance (Thagard, 1998b, p. 330). The papers that followed also name numerous collaborators, who aided in the gathering and interpretation of data: "It is thus obvious that the research that produced the evidential support for the bacterial theory of ulcers is not the product of individual minds working in isolation, but required the cooperative work of many teams of scientists" (Thagard, 1998b, p. 331).[33]

[33] While Thagard does describe a primary role for the community in enabling the process of discovery that led to Marshall and Warren being awarded the Nobel Prize, he separates that community role from the serendipity of the discovery in his description. That is, "serendipity," for Thagard, describes the original "discovery" of *H. pylori* in human stomachs, but not the later "discoveries" of the bacteria's correlation

Beyond the assistance of others in performing experiments and collecting data, personal contacts with other members of the epistemic community enabled the sharing of knowledge through the dissemination of results. Colleagues from other institutions guided them to good venues for presenting their results, and co-authored publications (Thagard, 1998b, pp. 332–333). While gastroenterologists were not initially persuaded by Marshall's claims, the community of microbiologists had less trouble accepting his and Warren's report, as it did not conflict with any dominant theory in that epistemic community. This acceptance by another scientific community generated the replication of results, as microbiologists began recording and publishing their observations of the stomach bacterium. Consequently, "[t]he growing recognition of the importance of Marshall and Warren's research made gastroenterologists take it more seriously" (Thagard, 1998b, p. 333). Thus, it was not Marshall's passion alone but also his epistemic agency, constituted by the willingness of a network of scientists to collaborate with him as well as to corroborate and share the knowledge he produced.

Thus, while a serendipity narrative constructed mainly around the role of Marshall creates a feeling of necessity about the events included and specificity about the role of Marshall and the importance of chance in enabling him and Warren to make their observations, this is a reflection of the retrospective construction of a narrative. The chance observations of

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with stomach ulcers or that *H. pylori* infections—and ulcers—can be treated with antibiotics. He later argues those "discoveries" were made by different methods (namely, "search" and "questioning"). The full description offered by Thagard is, "the discovery of *Helicobacter pylori* is best described as the result of serendipity and surprise, which produced questioning that led to search that produced more questioning that generated the recognition of a new species of bacteria" (Thagard, 1998a, p. 115). Thus even the "discovery" he suggests is marked by serendipity is serendipitous only at its origin, as one method that led to other methods that in turn generated the discovery. The tripartite approach to serendipity, however, requires that the valued outcome be determined before serendipity can be assessed. While in hindsight Thagard can limit the role of serendipity to the origin of the discovery process, it is the fact that the chance observation led to a valued medical discovery that makes it serendipitous—and the topic of two lengthy articles by Thagard. Thus, Thagard considers serendipity to be one *method* among others in a *series* of discoveries, whereas I argue that serendipity is a *descriptive category* applied to *a discovery process* as a whole.

Warren and the sagacious insight of Marshall were not sufficient for serendipity until the valued outcome had been determined, in keeping with my tripartite account. Further, features of his epistemic community—a network of collaborators, the sharing of knowledge through publication and presentation, and interaction between members of different scientific disciplines, for example—enabled Marshall to exercise the epistemic agency needed to follow up on an unexpected observation and to achieve a valued outcome.

3.2 Sir Alexander Fleming and the Discovery of Penicillin

The discovery of penicillin is the most well-known example of serendipity, given as a paradigmatic example in virtually every discussion of the concept in the literature and popular culture. Fleming was awarded a knighthood, among other prizes including the Nobel, for his role in the discovery of one of the most widely used and medically significant drugs known today. It is unquestioned that he played this role by chance. However, the story is more complicated than the prevailing narrative as it is shared in its simplest form, that Fleming "discovered" penicillin in the moment he made his unexpected observation. Narratives that describe Fleming as the serendipitous discoverer of penicillin often imply a linear, progressive, series of causes that inadequately represents the true story.

Fleming worked as a bacteriologist at St. Mary's hospital in London, England. One September, he left a number of petri dishes in a sink, dirty with the remnants of the cultures of the streptococcal bacteria he had been cultivating in them, whilst he went on vacation. Upon his return, while cleaning up and perhaps during a conversation with a colleague, he noticed that a reaction had occurred in one of the dishes—an unfamiliar mould apparently had landed, by chance, on the medium and grown there. More importantly, the unfamiliar mould had destroyed the resident bacteria where they came into contact with one another. Fleming recognized the

significance of this effect. In fact, he had seen something similar before, when he had witnessed the same (lysosomic) effects of his own tears on a bacterium, when a tear fell accidentally into a cultured medium.[34] The unfamiliar mould in this particular petri dish was later identified as *Penicillium (P.) notatum*. When refined, the agent responsible for the mould's antibacterial properties became a most useful therapeutic drug, the antibiotic penicillin.

The Nobel Prize for the discovery of penicillin was awarded jointly to Fleming, Howard Florey and Ernst Chain. From Oxford, Florey and Chain did the work to refine Fleming's mould and to establish it had therapeutic properties when taken by humans as a drug. Further, Florey travelled to America in a successful effort to mass produce and distribute that drug as an antibiotic to patients. While Fleming published a paper on the observations he made while experimenting with *P. notatum*, he had only gone so far as to produce a medium using the 'mould juice' to isolate certain types of bacteria, useful in his work developing vaccines (Fleming, 1980). Florey and Chain obtained a sample of this medium, and from this they were able to refine and test penicillin, ultimately leading to its mass production and clinical use.

3.2.a Penicillin as a Serendipitous Discovery

When accepting the Nobel Prize, Fleming stated,

> In my first publication I might have claimed that I had come to the conclusion as a result of serious study of the literature and deep thought, that valuable antibacterial substances were made by moulds and that I set out to investigate the problem. That would have been untrue and I preferred to tell the truth that penicillin started as a chance observation. (Fleming, 1964)

[34] As an entertaining side note, this apparently led to Fleming extracting the tears of colleagues in the lab to further test the effects of that bodily fluid.

Chance played two key roles in the observation of the petri dish that begins the typical narrative of the discovery of penicillin. First, it was chance that the mould, *P. notatum* landed in the petri dish and had its infamous effect on the bacteria therein. The dish was not intentionally placed with the aim of catching a random mould, let alone that particular mould. Rather, it was discarded in a sink, left to be cleaned when time allowed. The mould itself, *P. notatum*, is fairly rare. It apparently drifted up the back stairwell, through a door that was typically left open in Fleming's lab, from a lab on a floor beneath it.[35] The conditions that particular mould required to grow in the medium in which Fleming had been cultivating his bacteria samples were also rare, in that part of the world. The temperature rose and fell during Fleming's vacation in an unusual but exact pattern, allowing the streptococci bacteria Fleming had been cultivating to grow first, which fortunately happened before *P. notatum* landed in the dish, so that the mould could have its observable effects (see Hare, 1970).

Second, the fact that Fleming observed and took note of the mould's effects was partly a matter of chance. It is in particular for this that Fleming is often considered insightful, for having seen something significant in a place where nothing significant was expected. The narrative suggests that Fleming was cleaning up the petri dishes, or that he was conversing with a colleague, when he noticed the mould and its effects and thought or said aloud, something like, "that's funny" (Diggins, 2003, p. 247). Some earlier biographers (e.g., L.J. Ludovici, *Fleming, Discoverer of Penicillin,* 1952) suggest that Fleming knew in that moment that the mould would have significant value as a therapeutic agent. However, his sagacity is more generally captured by attributing to him the simpler insight that the petri dish, despite being contaminated,

[35] Versions of the popular narrative often claim that the mould blew in through a window. As his former assistant Ronald Hare points out, however, at that time the windows in Fleming's lab did not open.

contained a potentially significant discovery. That is, he is commended for not missing an epistemic opportunity, when others likely would have.

3.2.b Fleming's Sagacity

The sagacity of Fleming in this instance is normally framed in terms of his personal, intellectual preparedness. For example, Fleming himself had made an observation six years earlier that prepared him to note the effects of *Penicillium* mould on his bacteria. He had cultivated a strain of nasal bacteria taken from his own, cold-stricken, nose; he subsequently (unintentionally) dropped a tear into that dish and took note of its effects—while it killed off the bacteria in the petri dish, he noted that whatever was having such an effect did not damage human tissue as well, it having originated from his own eye (Fleming, 1945). This prepared him to observe similar antibacterial effects in the dish where *P. notatum* had by chance taken up residence.[36]

But Fleming did not himself follow up on his observation in a way that led to the discovery of the antibiotic penicillin. Instead, Fleming's focus was on the mould's capacity to isolate other microbial agents, a capacity that aided his ongoing research into vaccines. In particular, Fleming developed and used "penicillin plates" as a medium to isolate the otherwise difficult-to-work-with bacterium *B. influenza* (Fleming, 1980). Further experiments, some in animals, gave insufficiently positive results to warrant continuing experimenting with the mould's possible therapeutic properties. The published results of this research did not attract

[36] Note that this prompts van Andel to categorize Fleming under the appearance of serendipity he identifies as "pseudoserendipity": because Fleming already had lysozyme in his mind, Fleming was on track to recognize the effects of the P. notatum in his petri dish, and thus it is not a case of "positive serendipity" as commonly asserted (van Andel, 1994, p. 639). However, psychological difference between preparedness and being on a particular research track is a threshold or so-called "Sorites"-type problem that is outside the scope of this dissertation.

much attention when first released (although the 1929 article has since become a classic).[37] One of the editors of this journal at that time, however, was his soon-to-be co-discoverer, Howard Florey of Oxford.

What enabled the contingent connection between Fleming's observation and the discovery of penicillin was Fleming's agency within his epistemic community. Fleming had made his penicillin broth (or "mould juice," as he called it) available to students at St. Mary's. One of those students later used the broth to cure several newborns of their eye infections in Sheffield, where Florey was appointed at the time. Florey's later recollection of this event and Fleming's publication, as well as the fortuitous availability of a transfer of the broth in an Oxford colleague's specimen collection (obtained for research on bacteriophage), encouraged Florey and Chain to investigate the mould's therapeutic potential (Henderson, 1997, pp. 684–685). Thus Fleming's role as a lab director, teacher and member of a scientific community led to his unexpected observation resulting in the discovery of penicillin. In a scientific community, using one's agency to share results among colleagues, as Fleming did, can create connections between the research interests of members of the community that can enable serendipitous discovery.

The actions taken by Fleming in this case do not seem to differ greatly from the normal practice of science, unlike the notable self-experimentation undertaken by Marshall. Fleming did not himself pursue what were to become the most important properties of the "mould juice." He was unable to concentrate or stabilize the active ingredients sufficiently himself and seems to have had little reason to believe it would have the dramatic therapeutic effects later revealed by the work of Florey and Chain. Fleming himself states in his Nobel lecture: "My only merit is

[37] Reprinted, for example, in the *Reviews of Infectious Diseases* 2, 1(1980): 129-139 and in the *Bulletin of the World Health Organization* 79, 8(2001): 780-90.

that I did not neglect the observation and that I pursued the subject as a bacteriologist" (Fleming, 1964). De Rond (2014) hints that Fleming was legitimate in feeling he did not deserve such recognition for seeing a meaningful connection that simply "made perfect sense" between his unexpected observation and what he already knew and found interesting about antibacterial substances (p.6).

The actions Fleming took to preserve the mould in a way that others could take up its investigation were the actions of a "good bacteriologist" as he suggests, and not especially extraordinary (Bentley, 2005). These actions demonstrated that *P. notatum* had antibacterial properties; knowledge of these properties later went on to support the hypothesis that penicillin could fight infections in humans. Fleming's insight was in seeing the potential value of the mould he had found. He did put it to use himself, in the course of his own work, but the work he did that enabled the discovery of penicillin to happen was the dissemination of evidence about its antibacterial properties. Actions enabled by his epistemic agency made his original observation and insight accessible to others who were both willing and able to follow it up.

In fact, the only thing picked up and taken forward by Florey and Chain, it could be said, was the preserved mould itself. They used only the original observation and the knowledge that the observed effects had been confirmed, which had basically the same content for them as it had for Fleming at the time he made the observation. Further, Fleming's publication left out details about his methods that made it difficult for others to repeat his experiments, and he ceased his investigations into the therapeutic potential of penicillin without having obtained positive results. [38] As well, he did not publish findings that suggested his "mould juice" had

[38] The trouble with recreating the results seen by Fleming in his petri dish was twofold. First, it is practically impossible to recreate the conditions for achieving the same effect Fleming first witnessed unexpectedly (Kohn, 1989). Second, details about the work biochemists Frederick Ridley and Stuart Craddock had done with penicillin were left out of his publication, so that other scientists could not properly pick up from where they and Fleming had left off (Macfarlane, 1984, p. 142).

clinical value. For instance, Fleming once observed a colleague's eye recover from a bacterial infection when inundated with a fluid containing penicillin. He did not publish this observation, and may not have done so because he had been unconvinced by this "clinical experiment" (Macfarlane, 1984, p. 140). Therefore, Fleming did not make the discovery of penicillin. Nor did he do the work to bring his observation to fruition as that discovery. But he *did* contribute to the discovery process indirectly (and contingently) as a result of the access other scientists *did* in fact have to the knowledge he *did* contribute about penicillin.

Serendipity goes beyond the instant in which a sagacious person makes an unexpected observation. Serendipity includes the actual implications of that person having made that observation in the social and epistemological context at hand. In Merton's terms, the contribution of the researcher to the strategy aspect of the serendipity pattern is to make the connection between what is known and the unexpected observation, *and* to add to or otherwise change theory. But adding to or otherwise changing theory is not a purely epistemological action—it requires epistemic agency and for the conditions to be right for the epistemic community to take up that particular insight from that particular person.

3.2.c The Narrative of Discovery

Perhaps even more so than in the case of Marshall and the discovery of *H. pylori*, it is possible that the discovery of penicillin the antibiotic we know today *might not* have come about as a result of Fleming's actions. For example, others had already made observations similar to Fleming's while working with the *Penicillium* mould. Fleming himself once commented in a radio interview that, "but for circumstance, [his contemporary, Gratia] may well have been

the discoverer of *Penicillin*" (de Scoville, De Brouwer, & Dujardin, 1999, p. 258). Indeed, Gratia might have been given this credit, had he preserved the sample later agreed to be of the same mould from his own earlier experiments and had the sample picked up by Florey and Chain been Gratia's instead of Fleming's (de Scoville et al., 1999). If the sample used had been Gratia's, a sample generated during the normal practice of science, the discovery of penicillin might not be known as serendipitous today.[39]

From the perspective of Fleming and his unexpected observation, we could say that it may easily have failed to become part of the narrative of discovery in two ways. First, as an *individual* he may have failed to recognize the significance of his own observation, or to take note of it for posterity, so that what would have been a chance discovery becomes instead a discarded anomaly. Fleming did not discard his petri dish, but he did fail to recognize its ultimate value. In retrospect, Fleming saw this as a lack of expertise and resources, suggesting that he failed to further investigate the therapeutic potential of *P. notatum* because he was neither a chemist nor an "active clinician" with patients available for experimentation (Fleming, 1964). But these factors only explain why Fleming himself failed to pursue his observation, and are insufficient an explanation for why the observation he did pursue might have failed to attain the status of serendipity.

Second, there is the kind of failure that can explain the approximate dozen years between Fleming's observation and the ultimate discovery of penicillin. The epistemic *community* to which an individual belongs may fail to take up her observation into a process of discovery, or to recognize it as potentially leading to a discovery, or scientists in a community may direct their energies to projects more consistent with prevailing norms. In Fleming's case,

[39] I say 'might' because numerous chance events occurred during the process of the discovery of penicillin, and so it is possible that the narrative would center around one of them instead.

the dominant discourse at his home institution, St. Mary's Hospital, included an emphasis on proceeding with one's investigations "according to reason" (the mandate of the hospital's director at the time, Almoth Wright).[40] Despite several experiments with *P. notatum*, Fleming uncovered no *reason* to predict its therapeutic potential, and could not justify moving forward in that direction. He did, however, have a use for the mould as an aid toward the research providing his main source of funding, vaccines, and so he developed it instead as an isolator of bacterial cultures (Diggins, 2003, p. 248). From the moment of observation and for several years following, the context in which Fleming worked played a key role in directing his investigations away from penicillin's most valuable application.

Thus, Fleming was led in a particular epistemic direction (away from therapeutic potential), and he employed particular investigative methods (putting his "mould juice" to use rather than refining it further), as a result of factors primarily having to do with his epistemic community and his role within it. He may have had the appropriate insight into how to further investigate his observation, but various external factors led his own research in a different direction.[41] Failures of serendipity are not always the result of a lack of perception or agency on the part of an individual researcher. An epistemic community can fail to encourage or take up a hypothesis proposed by an agent because that agent is perceived as an outsider to a biased community, because the predicted discovery is deemed worthless or impossible at the time, or

[40] See Ronald Hare, "The Scientific Activities of Alexander Fleming, Other than the Discovery of Penicillin," *Medical History* 27(1983): 347-372, for a description of the relationship between Fleming and Wright: "Fleming played little part in the thinking, because captains do not argue with colonels" (p.350).

[41] Ridley and Craddock were also pursuing the investigation of penicillin's properties and for similar reasons abandoned this path: they had to do their research (attempts to further isolate the active agent in the broth in order to test its effects in mice) in a hallway, outside of director Wright's office, where the only tap with enough water pressure for their needs was located. The hallway was narrow and frequently used, and Ridley and Craddock were large men (Macfarlane, 1984, p. 131). Diggins points out there is no "satisfactory explanation of the failure to carry out the crucial mice experiment," and both Ridley and Craddock moved on to labs elsewhere shortly thereafter (F. Diggins, 2003, p. 248).

because the way in which it came about—for example by chance—does not fit the accepted criteria for methods producing knowledge in that community. Whether an unexpected observation wisely pursued will result in a serendipitous scientific discovery remains underdetermined without considering the social-epistemological context. In Fleming's case, factors about that community and his place within its network of agents could (and did) lead his observation to be taken up by the community into a discovery process.

For instance, at the community level, dominant discourses often constrain whether an observation counts as serendipity, and changes in discourse can mean that past observations become known as serendipitous over time (or vice versa). Thus, the epistemic status of an observation is determined by its significance within an accepted discourse in medical research and practice. During the years following Fleming's observation and with the discovery and proliferation of the sulfonamides, medical discourse turned toward the potential for new agents to be antibacterial and therapeutic. Thus, Florey and Chain recognized the great value of the original observation, whereas Fleming and his contemporaries were more focused on penicillin's scientific, antiseptic or vaccine-related potential (Fleming, 1964). As well, the onset of the war, while at first presenting an obstacle to any large-scale testing of penicillin, ultimately created a great need for agents that could treat infections. In turn, this meant there was a source of funding for large-scale production and distribution in America. Florey's perseverance in travelling to America and in developing methods for its mass-production was essential to its evolution into the drug we use today. It was also necessary for there to have been acceptance, co- operation, and support from the relevant epistemic community for Florey's insight, agency, and perseverance to succeed in bringing Fleming's observation to fruition as a discovery.

As a result, it is a matter of some debate whether Fleming deserved the Nobel Prize for his role in the discovery of penicillin. Gwyn Macfarlane claims in his 1984 biography, for

example, that Florey and Chain were forgotten by the public in the years immediately following the discovery and manufacture of penicillin. F.W.E. Diggins suggests this is because of Florey's refusal to talk to the press in 1940, which directed their questions to Fleming instead (Diggins, 1999, p. 56). Fleming's role as a teacher and researcher enabled the contingent connections between his observation and the discovery of penicillin to arise, including the publication and reception of his results, the relationships he had with others, and the work he did to test and describe the properties of the mould he accidentally found. Thus, the value of Fleming's insight, the actions he took, and the community's recognition of his contribution to the discovery of penicillin were all influenced by his epistemic agency within that community.

From the perspective of the outcome (i.e., the discovery and manufacture of penicillin), we could say that the narrative of discovery may have been told in a way that excluded rather than rewarded Fleming for his role. Fleming recognized the potential importance of an unexpected observation, and he preserved and pursued that observation, all of which are actions that might earn him the credit for sagacity. However, he paid little attention to what was later recognized as the truly significant feature of his discovery. Fleming's observation is considered serendipitous because of penicillin's therapeutic effects, not because of his preferred use for it to isolate bacteria in the lab. The later use of penicillin to cure infection was the discovery that granted Fleming's observation its status as serendipity. If there was no contingent connection between Fleming's unexpected observation and the development of the clinically useful drug, penicillin, then despite meeting the basic criteria for chance and sagacity, Fleming's unexpected observation and sagacious response would not be considered the origin of that discovery, and he would not in turn be known as having made a serendipitous discovery.

As later biographies reveal, the use of *Penicillium* mould to kill bacteria was introduced, studied, and even published before Fleming. Moulds have been used since ancient times in

various remedies, as a poultice or ingested, to treat wounds in the battlefield and beyond. In 1871, Joseph Lister named the mould *Penicillium notatum*,[42] and in 1882, he successfully treated an infected wound with it—Lister performed his experiments at the very hospital where Fleming later made his famous observation (Macfarlane, 1984). In 1897 Ernest Duchesne published his thesis on the antibacterial effects of mould; it has been said that Fleming went no further in his investigations of the mould than Duchesne did before dying of tuberculosis while still in his youth (de Rond & Thietart, 2007, p. 548). Merely years before Fleming's observation, in 1920, Andre Gratia and Sara Dath published the first journal article on the antibacterial effects of a *Penicillium* mould (de Scoville et al., 1999). For these and other reasons, some authors insist that the popular history of the discovery of antibiotics needs to be rewritten and credit redistributed (e.g., Crease, 1989). Thus while an outcome determines the narrative to be constructed, it does not prevent that narrative from changing.[43]

Consider, for example, the case of "Mouldy Mary." Mary Hunt was searching for a better mould to mass produce penicillin with, and happened to find it on a cantaloupe at the local grocery in the small town where Florey had taken the penicillin research, despite the lab having brought in samples of mould from around the world that had failed to produce penicillin in any greater amounts than Fleming's mould. Her find was essential to the ultimate success of penicillin as a drug, and thus to the discovery's value. She also did the appropriate epistemic work, by taking the cantaloupe back to the lab to investigate further. But her insight and actions

[42] The term 'penicillin' was first used by Fleming to describe the "mould juice" he used in his exploratory experiments (A. Fleming, 1929/1980).

[43] The current debate about Fleming and the discovery of penicillin is not centred on a dispute about the facts related to that process of discovery, but rather about how responsibility for the discovery (and the epistemic and other work that went into making the discovery happen) should be distributed.

did not earn her any awards or recognitions, except for a nickname shared in historical narratives of penicillin's discovery (Macfarlane, 1984, p. 211). [44]

Various events and individuals can play a role in a discovery process. Variations in narratives may recognize some people but not others, and over time these narratives may be revised to recognize people who have been missed in the past, or to emphasize the contributions of some people over others. A different narrative for the process of discovering penicillin (as with other discovery narratives) might have a different origin point, or include or omit certain events and individuals, reflecting the values of those who construct the narrative, for what purpose, and for which community.

This raises the consideration of Fleming's epistemic agency, the apparent reason for his inclusion in this narrative of a discovery process. Fleming's epistemic agency within his community allowed him to take the time to follow up on his observation, to publish his findings and to distribute his specimen for use in other labs. Further, his epistemic agency was recognized by the community that included him in the narrative of discovery. Fleming was perceived by the community as a trustworthy scientist beyond his contribution to the discovery of penicillin. This perception led his fellow scientists to consider his insight an example of sagacity, rather than luck, even though it only led to a major discovery in the hands of others. He was recognized with a Nobel Prize for having and following up on that very insight, when others may not have. But he was also rewarded for being a trusted and well-known epistemic agent beyond his contribution to this discovery process.

[44] See also http://peoriahistorian.blogspot.ca/2013/04/we-called-her-moldy-mary.html. Accessed 10 May 2015.

In a case such as the discovery of penicillin, it is easy to see that the individuals credited for serendipity can be different people altogether than those who bring a serendipitous discovery to fruition. Because serendipity is a category applied retrospectively to discoveries, the outcome determines what events and which people are considered essential to the process of discovery. But the community's respect for the people involved determines whether their unexpected involvement earns the label of serendipity. That is, earning the recognition for sagacity for the epistemic insight and actions one has taken in response to an unexpected observation is contingent on the *epistemic community's perception* of *one's epistemic agency* and on the *actual outcome*[45] of one's insight and actions. It follows that so is the status of serendipitous for discoveries that originate in or are enabled by unexpected observations. Fleming and others are recognized as sagacious for actions taken that are no different than the actions they would have taken during normal research practice. This fact notwithstanding, they are recognized as contributing epistemic agents despite their luck in playing the role they did in a discovery process.

In this way, the recognition of sagacity entailed by an attribution of serendipity to an observation someone made by chance is the reflection of the esteem of the narrator (a member of an epistemic community) for the epistemic agency of that individual. Giving Fleming half of a Nobel Prize for enabling the discovery of penicillin is recognizing his sagacity in an obvious way. It is the community's (positive) response to the role he was seen to have played in a discovery process.

[45] In contrast to the projected outcome, suggesting a disjunct between prospective and retrospective assessments of sagacity (see Chapter 4).

3.3 Discussion

To return first to Barry Marshall, the tripartite account of serendipity draws out the complexity of his expression of agency in the process of discovery toward a cure for ulcers. Marshall contributed to the *H. pylori* discovery process first by demonstrating his insight and taking the actions he needed to produce and disseminate evidence that *H. pylori* was found in human stomachs and correlated with the presence of ulcers. He is *also* well known because he had the insight into his own agency and place within the community needed to take the right actions to complete the discovery process and to earn the status of sagacious discoverer. In recognition of this agency and the valued outcome of his actions, Marshall has been given the starring role in a popular narrative from the history of science.

When described retrospectively, Fleming's actions were sagacious as well—insofar as they enabled the later work of Florey and Chain. His insight in examining rather than discarding the petri dish, in recognizing potential value in the effects he was observing, thus grants him the status of sagacity because of the valued outcome they enabled. That is, Fleming was sagacious enough to see that he should preserve this strange and surprising mould for further investigation by someone, if not himself.

However, if we take a prospective stance, Fleming's sagacity was expressed by acting the way he always did, but this time he exploited a chance opportunity to produce knowledge. Although he may indeed have thought that the mould had potential therapeutic value, it is fair to say he had no inkling of the kind of revolutionary impact it would have on medicine and health that penicillin did. Thus, although Fleming exploited an opportunity to produce knowledge, he did not do so with a particular(ly) valuable outcome as his goal or hypothesis in mind. Rather, he continued to investigate the properties of the "mould juice" he derived from *P. notatum* because he thought it might lead to *some* discovery, and not in order to discover

penicillin. However, his insight and actions did *enable* the discovery of penicillin to come about as it did. The sagacity Fleming demonstrated, then, was not in making the discovery of penicillin but in enabling a scientific discovery to result from his unexpected but potentially significant observation.

The Fleming narrative easily brings out the implications of the fact that sagacity is both the recognition of an agent's insight and actions, and of their agency in the relevant community. Many narratives of serendipitous discovery in science trace a discovery directly to its origin, including some popular narratives told about the discovery of penicillin, in which Fleming is described as the drug's discoverer. But this is a result of constructing the narrative post hoc, with the outcome in mind, as a linear progression from origin to outcome. The Fleming-penicillin story demonstrates, however, that the agency exhibited by Fleming (prospectively and in response to his unexpected observation) overlaps with the agency he is recognized for exhibiting in narratives of the discovery (retrospectively and in relation to the discovery outcome). What he is recognized and appraised for is both having the agency to produce and distribute useful evidence about the antibacterial properties of *P. notatum*, and having the agency to be recognized for his efforts in the discovery narrative and with awards.

One further point about sagacity is raised by the comparison of the Marshall and Fleming narratives. Both Marshall and Fleming saw that an unanticipated observation had potential value and enabled a change in theory and practice, but in the Fleming case it took more than himself to complete the process. One could say that prospective sagacity was exhibited as much by Florey as by any other figure in the narrative of penicillin's discovery; Florey had the sagacity to perceive and pursue the value of Fleming's unexpected observation. It is not unusual, especially in the contemporary context of clinical research where multidisciplinary teams have taken the place of lone investigators, for even the original

observation and judgment that initiates a discovery process to involve the insights and actions of several people. Thus, while serendipity narratives often focus on the contributions of singular individuals, what earns those particular individuals credit for their sagacity can also be a feature (the insight and actions) of several people working together or on the same problem.

Finally, sagacity can be risky. Marshall gets much of his credit in the popular narrative for taking risks in his dogged pursuit of confirmation and community acceptance of his discovery. Fleming may not have taken such risks, but Florey certainly did. People such as Florey, Chain, Warren and others, who played equally significant roles in the discovery process but who were not the ones most closely associated with the original observation that occurred by chance, tend to be minimized in narratives of serendipitous discovery. But they also deserve epistemic credit for those discoveries. Limiting the attribution of sagacity to the person who made the unexpected observation can result in only one person getting the credit in a narrative of serendipitous discovery when several deserve it.[46] Such narratives, in turn, incorrectly suggest that scientific discoveries are made by individual scientists on their own, rather than within and with the help of scientific communities.

3.4 Concluding Remarks

In Chapter 2, I described how the three elements of serendipity interact with each other and with the context in which they come together to enable a process of serendipitous discovery. A serendipitous discovery process begins with or otherwise depends on an

[46] This, in turn, can perpetuate the inadequate 'genius' approach to scientific discovery, wherein discoveries are thought to be the creative and skillful work of individuals in isolation, rather than in teams, groups and communities (see Simonton, 2004).

unexpected observation, arising by chance in relation to the processes currently underway at the time the observation is made, and by chance in relation to the expectations of the observer. That observer, in turn, expresses her sagacity by both perceiving the potential significance of the unexpected observation and by actually contributing that observation as a strategic datum to the community and to the process of discovery itself. Sagacity is properly conceived of in terms of epistemic agency: having and following up on an insight requires agency, and having one's insight taken up into a process of discovery depends on one's epistemic agency as perceived by the community that takes it up. Finally, an outcome valued by that community, the third element in serendipity, confirms the insight and validates the actions of the observer, showing them to be sagacious in hindsight as well as enabling the completion of that particular process of serendipitous discovery. However, these three elements and their interaction are shown only by retrospective analysis.

The differences between the narratives I have examined in this chapter highlight the fact that the agency involved in the insight and actions that go into producing and disseminating evidence—the epistemological contribution to the discovery process—occur in advance of the discovery's characterization as serendipitous. This raises the question of how a researcher or community can know which unexpected observations are worthy of his or their attention, independently of (or before) the valued outcome can be determined. Answering this question requires adopting a prospective, rather than a retrospective, approach to serendipitous discovery, as I do in the following chapter.

Chapter 4 –
Prospective, Potential Serendipity

In this chapter, I argue that there are causal factors that enable serendipitous discoveries to occur and describe those factors. In general, the kinds of factors that foster serendipity also increase a community's openness to unexpected opportunities for discovery, support the agency of its members, and improve access to and the sharing of knowledge. These community-level causal factors suggest that: some kinds of epistemic communities are more likely to produce serendipitous discoveries than others. The account of serendipity given here thereby differs from the definitional account of serendipity given in Chapter 2. The definitional account of serendipity offers definite criteria that can be used for *retrospectively* identifying when serendipity has occurred in a process of discovery. In this chapter I consider *prospective* and probabilistic causes of serendipity.

I begin by looking to the philosophy of science for how serendipity has been used by others to theorize scientific discovery. In particular, Aharon Kantorovich has used serendipity to explain how progress is made in science; serendipity is seen as a disruption of normal practice, introducing novelty into routine processes. On the other hand, serendipity arises out of the epistemological context of scientific practice, and so while it is unexpected it is not a matter of trial and error; it may be "cultivated" (Kantorovich, 1993, § 5.6). Finally, I look to explanations for why serendipitous discovery occurs within modern scientific epistemic communities.

Second, I propose general, probabilistic, causal conditions for serendipity. Drawing from the literature of computer science, organization theory and biology, I describe methods that have been suggested for cultivating serendipity. These methods can be subsumed under more

general categories: increasing opportunities for unexpected observations to be made and taken up, supporting the agency of community members, and improving access to knowledge.

Finally, I consider what this means for assessing the value of an unexpected observation when it occurs, and thus whether the insight into its potential value is likely to be proven correct. I argue that the standards by which opportunities can be assessed as worthy of exploiting are set by the epistemic community in which the process of discovery will take place, and I provide examples to illustrate this point.

4.1 Definitional vs Causal Accounts

The analysis of serendipity undertaken so far has focused on understanding what the category of serendipitous discovery describes. I have argued that three necessary elements—chance, sagacity and a valued outcome—must come together for a discovery to be serendipitous. What brings these three elements together in a process of discovery are features not of the three elements themselves, but rather of the community in which they occur. A chance opportunity for knowledge production is taken advantage of because a community perceives serendipity as a legitimate source of discovery, and because the observing individuals can and do exercise sufficient epistemic agency to recognize and act upon its significance. The observing individuals are able to express sagacity by following up on their insights about an unexpected observation only when their efforts are supported by relations of trust with fellow members of their scientific community. The valued outcome that retrospectively identifies a chance observation as serendipitous is valued by a community, and the process of its discovery is completed by that community. It is only when the discovery process is complete that a narrative becomes available to articulate the details of the network of various individuals and events that made the discovery possible (e.g.: Fleck, 1979). Thus, the definitional approach to

serendipity can only be applied in hindsight.

A causal account of serendipity, on the other hand, should provide the means for assessing when the conditions are right for that confluence of chance, sagacity and a valued outcome. In the philosophy of science, the positivist distinction between the contexts of discovery and of justification traditionally suggests that there can be no normative assessment of the context of discovery (e.g., Reichenbach 1938). In contrast, in this chapter I argue that some communities will tend to make a greater number of serendipitous discoveries. There are ways that communities can "cultivate" serendipity (Kantorovich, 1993). The structure of a community, the physical institutions that instantiate it, and the approaches it takes to knowledge-production influence how many chance observations are made by its members, as well as how often those observations are taken up into processes of discovery. Thus, there are normative claims to be made about how communities ought to be structured if they want to make (more) serendipitous discoveries.

4.2 Serendipitous Discovery in the Philosophy of Science

Kantorovich is the philosopher of science who has devoted the most attention to how serendipity may be fostered, with a focus on the community of practicing scientists. He argues for using the term "cultivation" because there can be no method, in principle, for "generating serendipitous discovery, since a discovery generated by employing a method which is directed towards the particular product of discovery cannot be unintentional [or unexpected]" (Kantorovich, 1993, pp. 21, 168). Rather, like when planting a seed one cultivates the soil so that it provides the conditions for the plant's growth but does not guarantee that plant will grow, the conditions for serendipitous discovery can be prepared, but this does not guarantee a serendipitous discovery.

While other philosophers have also referred to chance discoveries, Kantorovich goes further by giving serendipity the pride of place in his evolutionary epistemology of science. Kantorovich relies on Darwin's theory of evolution by natural selection as his model, and sticks closely by it when describing how science progresses by evolution as well. In Darwin's theory, genetic mutations occur within members of a species group; these mutations are random in relation to the adaptive needs of the individuals in which they occur. Nevertheless, some mutations will tend to enable the survival of the individuals who have them over others. For example, a mutation that modifies the shape of a beak that allows a bird to eat seeds from a wider variety of plants in its habitat will favour the survival of that bird when other birds may die because the plants they are otherwise able to eat die off. If birds with the mutation are thereby more likely to successfully breed than other birds, as a result of surviving longer, an increasing proportion of birds are likely to be born with that mutation as a variation. In time, if populations within a species diverge sufficiently enough from each other because of the accumulation of variations, a new species results. Thus, the evolution of species is caused by what Darwin called "natural selection" – the natural world "selects for" some variations over others over time.[47]

Kantorovich argues that in the context of science, serendipity acts as blind mutation, providing the most basic and essential means of progress to the evolution of scientific ideas and practices (Kantorovich, 1993). Chance discoveries input new knowledge from an unexpected source into scientific practice and theory, allowing the process of selection among ideas to

[47] This summary represents my own familiarity with Darwin's work, *On the Origin of Species*. For a readily available copy of this work, see the copy posted on the "Darwin Online" site: http://darwin-online.org.uk/content/frameset?itemID=F373&viewtype=side&pageseq=1. Accessed 18 July 2015. I'd like to thank Lisa Gannett for her attention to detail in reviewing the wording of this summary.

proceed and, thereby, science itself to progress. These processes of selection are not conscious efforts by scientists or the community. Rather, ideas that are selected are those that are most suited to the scientific context in which they are presented. For example, in simplest terms, no scientist will select for an idea about mythical beings as being valuable to science. Further, no community will select for a scientist's ideas if they do not fit with the prevailing, accepted norms for scientific knowledge. Selection, in Kantorovich's sense, is a subconscious sorting of potentially valuable scientific ideas from those ideas unlikely to be valued by the scientific community. Much of scientific progress, then, can be seen as the product of what are typically thought to be "a-rational" actions, according to Kantorovich, distinct from the products of conscious, rational thought (Kantorovich, 2014).

Importantly, while Kantorovich suggests that serendipity contributes blind mutations to the evolution of science, he does not see discoveries by chance as discoveries by trial and error, or random. Rather, because they arise within the scientific community and are perceived and potentially valued by that community, chance discoveries are epistemologically significant (Kantorovich, 1988). Epistemological norms, that is, guide the making of chance discoveries throughout. Progress is made because chance discoveries emerge from within the context of science, and they are thereby guided by the norms of science and so build upon the knowledge already attained by science (Kantorovich, 1988). My analysis so far has also shown that even the chance aspect of serendipity is guided by community norms and values.

It is not necessary to have an evolutionary epistemology of science to understand how the making of chance or serendipitous discoveries is epistemologically significant. Thomas Nickles, who was in large part responsible for fostering the post-positivist resurgence of philosophical interest in the context of discovery, also suggests that even chance discoveries arise out of the methods and theory of science. For Nickles, discovery relates to problem-

solving, which includes multiple methodologies, not all of which can be made explicit in logical terms (as propositions) (Nickles, 1978). Nickles thus describes the context of serendipity as the "rather normal work" of scientific practice (Nickles, 1997, p. 128).

According to Nickles, this is true of scientific discoveries generally: "What we retrospectively interpret as revolutionary breakthroughs typically begin life as rather normal work. Over time, by telescoping historical development, scientists whiggishly invest these charmed cases with far more meaning than they originally possessed" (Nickles, 1997, pp. 128–129). Nickles asserts that what is normally glossed simply as "a prepared mind" when explaining how scientists come by the appropriate insight into the significance of the anomalies they encounter is actually, a "whole process of hard thinking, of sorting out the issues and more precisely formulating the problem," and thereby deserving of more attention than typically given (Nickles, 1978, p. 29). In his words: "the received view treats hypothesis generation as a matter of active, informed guessing, but it places all the emphasis on the guessing and none on the information and reasoning which back it" (Nickles, 1978, p. 33).[48] Thus, Nickles challenges the traditional positivist distinction between an irrational and psychologistic context of discovery and a rational and logical context of justification.

But whether a particular process of discovery comes about is a social matter as well, dependant on aspects of a community beyond epistemic norms and the current state of knowledge. What is particularly interesting about Kantorovich, and Nickles (1994) agrees, is the addition of the community to our understanding of scientific discovery and serendipity. Kantorovich recognizes that serendipitous discovery happens at the level of the

[48] That is, hypothesis generation is not the result of trial and error; rather, as Nickles puts it, "Most scientists, I suspect, spend little time deciding whether to *believe* theory or model X, Y, or Z in a context-free manner. Rather, they typically appraise the *promise* of these models for work on their own, current problems" (Nickles, 1997, p. 129).

community, and factors about that community—what he subsumes under his conception of selection processes—determine, along the way, whether an unexpected observation will be taken up into a process of discovery. However, the recommendations he makes for how the scientific community might better foster serendipitous discovery fail to fully take into account the role of epistemic agency—that is, his epistemological recommendations are insufficiently social.

In particular, the recommendation he makes to the scientific community, to increase the freedom of individual scientists to pursue new ends with their research, demonstrates the narrowness of his concept of serendipitous discovery in science as compared with the description I offer:

> The next advice, which is directed to the scientific community, is to encourage freedom of research … According to this principle, good science should not be controlled by preconceived goals … Hence, we arrive at the seemingly paradoxical conclusion that in order for society to benefit from science, science should not be forced to solve the problems of society or to be controlled by society … basic research should not and cannot be directed from outside the realm of science. (Kantorovich, 1993, p. 169)

First, this quotation illustrates that for Kantorovich "good science" is not influenced by extra-scientific goals; the science he is referring to is basic science, and as such it may be that it has its own ends and should not adopt the ends of other disciplines. However, serendipity does not only occur in basic scientific research—it also occurs in scientific practice that is guided by practical and social values. Thus Kantorovich's claims that we should narrow the scope of science has the second effect of raising the question of the status of serendipitous discoveries in areas of research with extra-scientific goals that nevertheless require the practice of "good science" to be achieved, such as in clinical research. The characteristics of a scientific community

that fosters serendipitous discovery, as I will show, are not limited to characteristics that are epistemological, nor to communities made up only of basic scientists.

Further, as I will demonstrate in the rest of this chapter, values beyond epistemological norms and epistemic goals influence a community's ability to make serendipitous discoveries. Isolating science from society and approaching research as an individualistic enterprise run contrary to methods for enhancing the scientific community's ability to make serendipitous discoveries.

4.3 Causal conditions for serendipity

Despite the fact that serendipity arises by chance and thus cannot be predicted, there are things one can do to make serendipity more likely to occur in one's life, and there are things that organizations can do to increase the likelihood that they will reap the benefits of serendipity through innovation. But, because serendipity by definition emerges by chance, there can be no set of necessary and sufficient conditions out of which serendipity will certainly arise. McBirnie identifies this as the "paradox of control" inherent in the concept and experiences of serendipity (McBirnie, 2008). Serendipity is a process and is beyond the control of any particular person. Process introduces unexpected observations; chance cannot be controlled by the individual observer. Serendipity is also about perception. Perception of an unexpected observation as potentially valuable and worthy of one's attention, is a subjective determination (McBirnie, 2008, p. 606). The perception of potential serendipity is also often considered a skill that some people have more than others, and that can be honed. Thus, while the process of serendipity seems to be beyond control, the perception necessary for a process of serendipitous discovery to arise out of that process, in response to the unexpected observation generated by that process, seems to be within control (McBirnie, 2008, p. 611).

However, while the processes that generate serendipity may be beyond an individual's control, they are somewhat controlled by the broader community that sets the context in which those processes occur. In science, for example, serendipitous discovery arises out of the norm-driven practices of science. Some practices will be more likely to cause unexpected observations to be observed by researchers than others. Further, as I will show, some types of communities will make it more likely that such unexpected observations are perceived and judged worthy of attention by their members.

The causes by which chance, sagacity and a valued outcome are brought together are probabilistic. While it is not possible to say prospectively that, given certain facts, serendipity will definitely arise, it is possible to say prospectively that, given certain conditions, serendipity will more probably arise. Therefore, a community that wants to foster serendipitous discovery will organize itself in a way that increases the probability of serendipity.

Methods for encouraging serendipity have been formulated as practical suggestions for particular communities. Computer scientists wish to program serendipity into their search engines, so that they can create opportunities for surprising discoveries for people who use them. Organizational theorists wish to understand how to encourage serendipity because they see it as a method for increasing innovation in business. Biologists argue that biological field stations are "sites for serendipity", and as such they should be modelled. Specifically, I argue, as generalizable goals, there are three key ways a community can improve the probability that serendipitous discoveries will come about. First, a community and its members ought to be open to the possibility that knowledge will arise from an unexpected source and be prepared to facilitate the likelihood of such occurrences. Second, networks among members of communities ought to exist and be encouraged to support the epistemic agency of those members. Third, a community ought to share new knowledge

amongst its members by promoting and maintaining access to that knowledge.

4.3.a Openness to Unexpected Observations

As programmers, the aim of computer scientists has been to design software that increases the probability that an information seeker using that software will make a serendipitous discovery. Some have claimed that serendipity will be increased primarily by increasing the number of unexpected opportunities that an information seeker will encounter. Programs designed for this enable a greater number and wider variety of connections between data to be found while searching (Figueiredo & Campos, 2001, p. 122). However, increasing the probability of serendipity entails more than simply increasing the number of chance observations available. It requires the uptake of those observations as part of the process of discovery.

Merton and Barber (2004) devote a chapter—"Moral Implications of Serendipity" (pp. 149-157)—to explore the evaluative force of serendipity as a label. Merton and Barber point out that, "[u]nless there is a special set of explanations and justification of chance success and chance failure, the intervention of chance will impugn the basis of skill and responsibility on which estimates of such an individual's competence rest" (Merton & Barber, 2004, p. 154). In fact, many researchers won't expose the accidental origins of their discoveries until their reputations are safely in hand (Alcock, 2010; Campanario, 1996, p. 7). The moral implications of serendipity depend on whether knowledge can arise by chance, or outside of the control of the

knowledge-producer. When chance is considered an illegitimate means of producing knowledge then people are unlikely to use serendipity to describe their discoveries—such as in scientific publications. A further consequence of this is that serendipity is then perceived, in light of its paucity in descriptions of discoveries, as special or rare. People in such communities may not expect to make unexpected observations. As well, unless an epistemic community accepts that valuable discoveries can be made by chance, its members will not be supported when they wish to follow up on an unexpected observation.

In fields where chance discoveries are more common and acceptable, serendipity is more likely to be common and accepted as a source of knowledge. While tracing the history of the word "serendipity", Merton and Barber note that its dispersion happens more quickly in fields where there is a structured acceptance of uncertainty and happy accidents (Merton & Barber, 2004, p. 156). Other fields that emphasise rigorous controls and standardized methods in the production of knowledge may be less likely to believe chance can generate legitimate discoveries and that those who make such discoveries deserve professional recognition and reward (Merton & Barber, 2004, p. 157). A series of lectures by representatives of different fields of research given at Darwin College (UK) in 2008 show that some fields (such as astronomy) are more accepting of serendipity as a mode of discovery than others (such as physics) (Fabian, 2010; Friend, 2010). In his study of 400 of the most-cited papers in the history of science, J.M. Campanario argues that more observational sciences are more accepting of serendipity than sciences that emphasize experimentation and thus control (Campanario, 1996, p. 5). From the perspective of process, some community norms will enhance the probability that serendipitous discoveries will be made by those communities.

Whether serendipity is valued as a source of discovery by a community also makes a difference to whether individuals who encounter things unexpectedly perceive their potential

value. An environment in which serendipity is praised as a source of discovery will more likely encourage individuals to pay attention to unexpected observations that may be of value. For example, Makri and Blandford suggest that "reflecting on their experiences [with serendipity] in interview was likely to make [their respondents' minds] more 'prepared' for making and exploiting future serendipitous connections" (Makri & Blandford, 2012a, p. 16). That is, the very act of encouraging the taking advantage of opportunities may make more unexpected observations present as unexpected opportunities for discovery.

The prepared mind that can recognize an unexpected opportunity as such is commonly regarded as a property of the individual. Empirical researchers Allen Foster and Nigel Ford suggest that some individuals are "super-encounterers," who have the methods and skills at hand to create "situations conducive to information encountering" and who "share a common excitement for information encountering" (Foster & Ford, 2003, p. 325). Simonton delineates three common characteristics of scientists who demonstrate creativity in making discoveries: they have dispositional traits that make them more open to new experiences, they have less conventional developmental experiences, and they behave in ways that belie a wide variety of interests and involvement in various activities (Simonton, 2004, pp. 172–173).
However, as Kantorovich suggests, the "mind" of the community must also be prepared, for it to take up the discovery process (Kantorovich, 1993, p. 182). It is the values of the community as a whole that determine the acceptability of its members' perceptions of unexpected opportunities as worthy of following up.

For example, individuals who work in an encouraging environment are less likely to develop what some have called "blinders" (van Andel, 1994) or "serendipity filters" (McBirnie, 2008). McBirnie explains "serendipity filters" as the reason for occasions when a person recognizes the potential value of an unexpected observation and yet ignores it. She points out

that the recognition of an unexpected observation as potentially significant does not always lead a person to confirm her luck by confirming its value. McBirnie conducted interviews with jazz musicians and academic researchers about their experiences with serendipity.[49] She notes that while participants generally acknowledged they could not help but notice that the unexpected observation could be serendipitous when it occurred, some participants "recounted much less willingness to change direction than others" (McBirnie, 2008, p. 608). McBirnie suggests that these individuals seemed to experience pressures—including their needs, responsibilities and the limitations of their environment—that tended to act as a "serendipity filter" affecting the perception of serendipity (McBirnie, 2008, p. 608; McBirnie, 2012, pp. 45–46). According to McBirnie, perceiving serendipity includes an aspect of judgment about whether it is appropriate to pursue and confirm the significance of an unexpected observation.

In many cases, pressures arising from matters of process can cause a researcher to judge that an unexpected observation is, comparatively, not worth pursuing. For example, Fleming felt the pressure of directing his research toward ends deemed worthy by his institution's director, and so he turned his attention back to his vaccine work and away from further exploration of *P. notatum*'s properties. Bernard Barber and Renée Fox describe two more examples of serendipity (almost) lost[50] in a 1958 article, "The Case of the Floppy-Eared Rabbits: An Instance of Serendipity Gained and Serendipity Lost." In the first example, the investigator makes an interesting and unexpected observation that a particular compound

[49] This research grounded the conclusions of her MA thesis in information studies and her 2008 article. McBirnie draws her examples for her PhD thesis (2012), a quantitative analysis of serendipity, from the *Citations Classics* Commentaries, a collection of short, autobiographical narratives requested from the authors of the most-cited papers in the history of science, detailing the discoveries those papers describe. They are now available online here: http://garfield.library.upenn.edu/classics.html

[50] As Barber and Fox note, publication bias, space restrictions and the overwhelming quantity of failed experiments prevent most experiences with 'lost' serendipities from generating publications, and therefore we have little record of them (Barber & Fox, 1958, p. 131). In the cases examined here, a valuable outcome—a contribution to theory about the action of enzymes on cartilage—was arrived at by one investigator interviewed, but not the other.

makes his rabbits ears flop in a dramatic and amusing way. He seeks and is unable to find an explanation for his observation. As Barber and Fox assess, "the element of creative imagination, which is necessary to complete an instance of serendipity by supplying an explanation of the unusual effect, is not yet present" (Barber & Fox, 1958, p. 131). The explanation for his turning away from the observation's pursuit includes factors such as his being "terribly busy working on another problem at the time" and his having "already used all the rabbits [he] could afford" (Barber & Fox, 1958, p. 131). Similarly, the second example is of another investigator working with rabbits who noted the same observation of floppy ears. He turned away from its pursuit because of preconceived ideas he had about ear cartilage and because his research was in general more narrowly focussed on muscles (Barber & Fox, 1958, p. 135). Thus, in these cases, the influence of the pressures of process, such as limited resources and time, affected the judgments of researchers as to whether an unexpected observation is worthy of their attention.

McBirnie notes that often, when a person filters out an unexpected observation and fails to judge it worthy of attention, an opportunity for serendipity is lost: "Although the unexpected information was occasionally stored for future use, it was more often brushed aside and lost" (McBirnie, 2008, p. 608). Members of a community in which serendipity is not valued are more likely to filter unexpected opportunities out by having other, preferred priorities.[51] Thus, communities should be organized in a way that resists the loss of potential serendipity when an individual researcher cannot, because of pressures, perceive its value or give it her attention. Beyond endorsing a positive attitude toward unexpected observations as sources for potential discovery, a community can reduce pressures that function as blinders.

[51] Related to this is McBirnie's observation from her dissertation research on the Citation Classics Commentaries that recognition is equally likely to occur in the moment of observing as it is to be delayed until some later time, when the individual retrospectively recognizes a chance event (in light of new insight or perspective) as having been or remaining potentially serendipitous (McBirnie, 2012, p. 334).

This does not necessarily indicate adopting an individualistic approach to freedom; individual freedom can be gained by sharing responsibilities among community members for paying attention to and following up on unexpected observations that may be of value. Networks and collaboration are one way of reaching this goal. Second, resisting the loss of serendipity may mean making observations accessible at a later time, or to other people, at which time or for whom they may be valuable. Therefore, sharing knowledge among community members, creating depositories of potentially useful knowledge, and disseminating knowledge are also key methods for enhancing a community's ability to make serendipitous discoveries.

4.3.b Networks and Supporting Agency

One area of study that has focused on delineating community-based conditions for encouraging serendipity is the field of organizational studies.[52] Authors in this literature, including de Rond, mark out the features of organizations and institutions that experience more serendipity than others. For example, Miguel Pina e Cunha, Stewart Clegg and Sandro Mendonça (2010) define serendipity as "the accidental discovery of something that, post hoc, turns out to be valuable" (Cunha et al., 2010, p. 320). Essential to the post hoc realization of something of value is the network or organizational context in which the serendipitous discovery takes place. Cunha and colleagues comment on "the importance of networks in being able to render the [observer's] surprise into something that is good and fortunate" (Cunha et al., 2010, p. 323). They further argue that teamwork is important "throughout the serendipitous process", and claim that "it is not just the merit of the discovery that counts *per se* but also the

[52] A colloquial example is the design of buildings for companies such as Google that intend to enhance innovation by cultivating serendipity: such designs emphasise the creations of accidental meeting places, for example, where employees who may not otherwise interact can and do. See for example Greg Lindsay's article in the New York Times Sunday Review column *Gray Matter*, "Engineering Serendipity" (April 5, 2013) <http://www.nytimes.com/2013/04/07/opinion/sunday/engineering-serendipity.html>

context in which it emerges" (Cunha et al., 2010, p. 325). By this they mean that organizations must be "mature" enough to accept new ideas, the political landscape has to be favourable to the new idea, and a discoverer ought to be "in an influential position at the creative moment or in receipt of support from powerful actors… All these factors may influence the fate of a discovery" (Cunha et al., 2010, p. 325). Thus, organizations that are open to new ideas, encourage teamwork, and provide support to potential discoverers will be more likely to take up and enable the completion of a process of serendipitous discovery.

Further, individuals are deemed to be trustworthy epistemic agents insofar as their actions are judged to provide epistemic value to the community. But, having the insight and ability to make epistemic contributions to science is also a reflection of how a scientist's agency has been able to develop within that community, or what contributions to the processes of science she has been able to make. Townley addresses the importance of trust among agents in an epistemic community. In Townley's framework, epistemic agents in a community will share responsibilities, each agent trusting other members of the community to have knowledge she does not have. Thus, trust is a key factor because of the need for cooperation in epistemic work. According to Townley, epistemic agents trust each other in several ways: to know what one cannot oneself know; to be reliable sources of knowledge; to teach; to inspire; or to otherwise guide one's own production of knowledge (Townley, 2011, pp. 8, 34). Thus, what enables one agent to trust another is not restricted to assessments of that agent as a source of knowledge. We do not evaluate the trustworthiness of epistemic agents by the knowledge they produce alone.

More specifically, as Townley argues, trust entails that one voluntarily remain ignorant about some things directly relevant to checking up on whether an agent actually has the knowledge she testifies to have. In cases of serendipity, this can be seen in terms of

trusting an investigator even though there is *no method*[53] for either assessing the hunch that investigator has that the unexpected observation she has made is significant and worthy of attention (Townley, 2011, p. 24). Thus, serendipity requires that the observing epistemic agent be trusted—for reasons beyond this particular potential contribution of knowledge to science—by her community.

Teamwork allows for the sharing of responsibility among prepared minds, multiplying the possibilities that someone will have the insight and background knowledge needed to recognize potential serendipity when it occurs. Kantorovich suggests that epistemic cooperation among modern scientists enables serendipitous discovery (Kantorovich, 1993, p. 160). Sharing ideas among collaborators increases the chances that research will develop in an unexpected direction. However, it is not only the researcher's epistemic agency that matters in determining whether and what contributions she will make, it is also the values of her community and, importantly, the social context in which she is making those contributions. For example, Marshall was able to continue his research when he moved to a new hospital to work, which required the acceptance of his colleagues, who dispersed the epistemic work amongst themselves in his aid. Fleming was given due credit for his role in the discovery of penicillin, despite the fact that he may have played a relatively minor role in relation to his fellow Nobel Prize winner, Florey, because the community had taken up his story and woven it into the discovery narrative (Macfarlane, 1984).

Epistemic communities, like computer programs and organizations, are social entities that exist in the physical world. Thus, openness to opportunities for learning, support for the epistemic agency of members, and access to information are goals that can be attained by

[53] Of course, the practice of rational reconstruction could be such a method; one can reconstruct a possible deductive path from a known set of factors to the conclusion or inference drawn—for example, one performs experiments to confirm an unexpected observation—but this is not an assessment of the inference itself or the 'hunch' that led to that inference, so much as a confirmation of the results.

establishing physical settings and institutional structures that are organized in ways more conducive to knowledge production. For example, William Michener and colleagues make a case for the value of biological field stations as sites for serendipity because they act as a "gathering place … for a rich diversity of highly creative and motivated scientists, students, and citizens" (Michener et al., 2009, p. 300). Field stations are often "in small villages where resident scientists and students interact far more among themselves and with non-scientists than they might normally do on a typical university campus" and thereby create a physical site where social networks are built (p. 306). As well, at field stations, a "wealth of data, physical and biological specimens, and publications" are secured (p. 306). As a consequence of having this physical space where people and data can gather, "preparedness of mind is fostered, enabling surprising discoveries of both scientific importance and social relevance" (p.301).[54]

Networks can also have a negative effect on serendipity, as noted by Toby Sommer when he developed a contrary concept from the same fairy tale, the *Princes of Serendip*. Sommer argues that it is equally important to have an allegory illustrating 'nulltiples' in science: nulltiples are "suppressed, unpublished discoveries" (Sommer, 2001, p. 77). He proposes what he calls 'bahramdipity', a name derived from the character of Bahram V Gur, the King of Persia who thwarts the efforts of the Three Princes of Serendip and others several times in the relevant collection of fairy tales (Sommer, 2001, pp. 78, 79–80). Thus, bahramdipity represents instances in scientific research of "the cruel suppression of serendipitous discovery," a phenomenon Sommer identifies as "well known but little discussed" (Sommer, 2001, pp. 77, 78). Examples of

[54] It is interesting that Michener and colleagues additionally argue that discoveries made this way are superior to other kinds of discoveries, in terms of both scientific importance and social relevance. For Michener et al., serendipitous discoveries may often be more valuable discoveries because the features of epistemic communities that make serendipitous discoveries more likely may also be features that encourage more valuable discoveries. This is too big a claim to argue for here.

this phenomenon given by Sommer include: (i) potential discoveries made, by associate scientists who find it "dangerous to question the skill or knowledge of a principal investigator" (p. 79), by those who are more concerned about producing the results the head of their project expects (pp. 79-80), and by junior faculty who resist giving their scientific opinion because they are concerned about tenure review (p.80); as well as (ii) discoveries squelched by research leaders who often seem oblivious to the fates of those whose careers they affect (p. 80). As Sommer illustrates, when the circumstances for serendipity arise in the practice of an agent who is prevented by the actions or attitudes of others from exercising her epistemic agency, it can be lost or left incomplete.[55] If conflicts between agents and hierarchical patterns of authority can suppress serendipitous discovery, then a supportive, diverse network should encourage it instead.

Paying attention to the networks that form within a scientific community draws attention to the ways in which individuals are either able to develop or are prevented from developing their epistemic agency. Networks can enable individuals to develop the very agency they need to have a particular insight and to be able to follow up on that insight to make a

[55] Note that while Sommer's examples suggest there is more involved than the activities and intentions of any particular figure of authority (that is, that implicit power structures or internalization leading to self-constraint may be at fault as much as any particular group or individual who can be picked out), he explicitly narrows the application of his concept and the definition he offers for bahramdipity focusses on exactly that: "**bah·ram·dip·i·ty** (bă' rŏm dip' ə tē) *noun*. 1. The suppression of a discovery, sometimes a serendipitous discovery, by a more powerful individual (bahram) who does cruelly punish, not merely disdain, a person (or persons) of lesser power and little renown who demonstrates sagacity, perspicacity and truthfulness to the bahram. 2. The self-serving promotion of an often unreliable discovery and its discoverer by a more powerful individual (bahram). [From Bahram of Persia, as characterized in the fairytale *The Three Princes of Serendip. cf*., serendipity.]" (Sommer, 2001, p. 80).

contribution to a discovery process. Serendipity crosses space and time and involves multiple individuals (McBirnie, 2012). A good network enables and encourages interaction between a greater number of epistemic agents in a community, thereby increasing the agency of network members by developing their ability to perceive unexpected opportunities for discovery and by supporting them in their efforts to contribute to discovery processes.

4.3.c Sharing Knowledge and Enabling Access

Evidence generated by serendipity for a hypothesis may or may not lead to a discovery. It is more likely to do so, however, if it is made available to those who know of the problem it might ultimately resolve. Networks increase the likelihood that someone will recognize the significance of an unexpected observation, and encourage the sharing of responsibility for taking up a process of discovery among members of an epistemic community. In like fashion, sharing knowledge itself can result in a greater probability of serendipity.

As with the example of cosmic background radiation, without the social structures that allow for interaction between academics and the sharing of their ideas, those who unexpectedly found the solution to the problem would not have been able to provide it to those who were trying to solve the problem. Susan Alcock, in a 2005 Darwin lecture, entertains the idea of why there was no concept like serendipity in the ancient world. She concludes that science at that time was competitive, reputations were based on disputation, and so there was little co-operative scientific work being done. “In a world of isolated scholars, often in competition, lacking a community of inquiry, of mutual exchange: in such a milieu new ideas and research trajectories could be generated, only to perish unnoticed” (Alcock, 2010, p. 16). The exchange of ideas and sharing of knowledge is essential to the fostering of serendipity.

Besides recommending the establishment of networks that "help serendipity flourish," Paul André (2009) emphasizes the importance to serendipitous discovery of maintaining and improving "domain expertise" and using a common language that allows for easy sharing of information between expert domains. A computer program can maintain and improve domain expertise by making more relevant information accessible to seekers, filling in gaps left in their knowledge by their preference for some topics over others by providing them with a full review of current domain-relevant knowledge. Using a common language across domains allows a program to create connections between knowledge quicker and more effectively. Establishing networks further enables the sharing of information across domains (André, 2009, pp. 20-21). These features of a computer search program—providing more and widely varied sources of information to seekers by increasing the data available, as well as making it more accessible by establishing a common language, and to more people via the establishment of networks—can be seen as features of an epistemic community.

Thus, dissemination of information about unexpected observations is part of contributing to serendipitous discovery. Better dissemination should result in more serendipitous discoveries, insofar as this provides others with opportunities to demonstrate the significance of an unexpected observation. In turn, as the computer scientists point out, having more information available increases the potential that connections will be made between an unexpected observation and current knowledge. This is more than having a better prepared mind in the individual making the unexpected observation. Rather, a more prepared community will allow for more opportunities to make connections and therefore will increase the number of unexpected observations whose significance may be recognized by community members. For example, as Michener noted in regard to biological field stations, the probability of serendipity increases not only when diverse researchers interact, but also when a depository of

knowledge—in Michener's case, biological specimens, records and data—is made accessible to diverse researchers. Accessibility also improves the probability that when a problem arises, the knowledge needed to resolve it is available to those who need it (Michener et al., 2009, p. 305). Improving access to knowledge increases opportunities for unexpected observations, the probability that such observations will be recognized as significant, and the probability that these will come to fruition as serendipitous discoveries. Thus, communities that share knowledge—through networks that enhance access to knowledge, support the agency of their members, and are open to the possibility that unexpected observations may give rise to valuable discoveries—will cultivate not only the conditions for chance, sagacity and valued outcomes but also for their confluence in serendipitous discovery.

4.4 Assessing the Potential Value of Unexpected Observations

As Kantorovich emphasises, the scientific community will only accept certain kinds of unexpected observations as potentially valuable and worthy of attention. For serendipitous discovery to occur in science and medicine, the unexpected observation must not only generate a valuable outcome, it must be valuable *to science* and *to medicine*. Increasing the number of unexpected observations available—or even the number of such observations that are perceived and given attention—will not by itself lead to more serendipitous discoveries. This is sometimes so even when the conditions are right for many of those observations to be taken up by the community. Only certain observations will ever be taken up at a particular moment in time; namely, those observations that are assessed to be of potential value. Moreover, only those observations that actually prove to be valuable will result in a serendipitous discovery. Arguably most important among the standards by which potential value and actual value are measured in science and medicine are the standards of evidence.

4.4.a Potential Evidence

In *The Book of Evidence*, Peter Achinstein (2001) distinguishes between several conceptions of evidence used in the scientific literature and in the philosophy of science. Achinstein argues there are two kinds of evidence that are important to scientists, what he calls "veridical evidence" and "potential [veridical] evidence." Veridical evidence is the kind of evidence that scientists ideally seek. According to Achinstein, if *e* is veridical evidence that *h,* then

(i) *e* is a good reason to believe *h*,

(ii) this is independent of whether anyone knows of *e* or *h* or believes that *e* is evidence for *h* (objective)

(iii) this is irrespective of the epistemic situation at the time or of the investigator (nonrelative),

and

(iv) *h* is true.

As well, veridical evidence does not preclude the possibility that further empirical evidence may be needed for *e* to be complete evidence for *h* (Achinstein, 2001, pp. 26–27).[56, 57]

Potential veridical evidence is similar to veridical evidence, having all the same features except for (iv): *h* is not necessarily true. Achinstein gives the example of spots on a child's face (*e*) as evidence that the child has measles (*h*). Spots on a child's face are indeed evidence that

[56] This distinguishes veridical from conclusive evidence, wherein *e* establishes *h* with certainty (p. 27).
[57] Note that evidence can be veridical and yet no one know that it is (due to its being objectively rather than subjectively veridical, it is so independent of anyone's knowledge). As well, evidence perceived as veridical because it can be disproven by new empirical facts can turn out to be only potential evidence after all (see the next paragraphs).

a child has measles, whether this particular child actually has measles or not. The child may have spots on her face and yet not have the measles. If a conclusive test is performed and the measles are confirmed, then spots on a child's face (*e*) meets the criteria and is veridical evidence for measles (*h*). Unless a conclusive test is done to confirm the measles, the spots remain *potential* evidence for the child's having measles (Achinstein, 2001, pp. 27–28). When *e* is potential evidence for *h*, the truth of *h* is not presumed. However, there is good reason to believe *h* (though in a weaker sense than in the case of veridical evidence), even if *h* later turns out to be false.

Potential evidence is objective and nonrelative; it holds regardless of anyone's beliefs and no matter the current state of knowledge. In cases of serendipitous discovery, potential evidence is contributed to a process of discovery despite its being obtained in an atypical way. Achinstein argues that potential evidence can give way either to being disproven or to becoming veridical evidence, depending on future empirical evidence for the truth of the hypothesis. His examples are the experiments done by Heinrich Hertz and by J.J. Thomson to demonstrate whether atomic particles carry a charge. Hertz's experiment demonstrated that atomic particles do not carry a charge, but Thomson's later, adjusted experiment demonstrated that they do. Hertz's experiment was exposed as flawed by Thomson, who changed a parameter in the experiment that both demonstrated the flaw and overturned Hertz's conclusions by producing different results. So, even though Hertz *seemed to have* good reason, at least in a subjective sense, to believe the results of his experiment (*e*) were evidence that atomic particles carry a charge (*h*), it turns out he did not have a good reason in an objective sense that is shared by veridical and potential evidence: "Flawed experimental, observational, or test results do not constitute a good reason to believe a hypothesis, even in a sense of 'good reason' that does not require the hypothesis to be true" (Achinstein, 2001, p. 28).

In contrast, in the case of serendipity, researchers are not initially in a position to believe that *e* is evidence of *h,* and yet that proposition may be true, and eventually known to be so. Since they produced that evidence with valid (not flawed) methods, as it turns out, the potential evidence is good evidence for the valued outcome, no matter what earlier projections of value might have been. This complicates Makri and Blandford's process model, presented in Chapter 2, but does not change it. I simply add that the projected value that enables the production of potential evidence may not be the same value that the outcome has. In either case, it is the value of the outcome, and not the projected value, that gives rise to the value of the potential evidence.[58]

To explain further, consider the fact that in normal scientific practice, a good reason to believe that *e* is evidence that *h* is obtained by rationally establishing an evidentiary relationship between *e* and *h* through experimentation. But there are cases where the person who makes the original, unexpected observation is not the same person who puts that observation to work as evidence for or against a hypothesis. For example, while Fleming first observed the antibacterial actions of penicillin in the mould he found in his petri dish, it was Florey and Chain who ultimately cultivated and produced penicillin. In such cases, the evidentiary relationship is enabled but not established by the person who produced the potential evidence unexpectedly.

[58] Here again we see the importance of a shared language. If potential evidence is produced by a community with a specific language for evidence (e.g., qualitative data), it can be difficult for other communities (e.g., those that rely on quantitative data) to put it to use. This limits the number of valued outcomes that evidence will be able to contribute to. Kantorovich points out that part of the reason for the success of serendipitous discovery in science is the community's reliance on mathematical, or deductive formulations for its theories (Kantorovich, 1993, p. 160). Mathematical formulas, as Kantorovich explains, can have uses beyond their original purpose, uses that often cannot be predicted. Kantorovich gives Planck's second law as an example. Thus math provides a shared language among scientific researchers; members of the community even outside the discipline of the person who created the formula are able to put it to use in novel ways.

Thus, the person who gets credit for demonstrating sagacity in such cases gets that credit for producing potential, but not veridical, evidence. Further, this person gets credit for having produced potential evidence despite not necessarily knowing the outcome of that production—that is, without knowing for what it is potential evidence.

Therefore, the appropriate method for assessing whether an unexpected observation is worth following up is to assess, minimally, whether it presents an opportunity to produce potential evidence. Serendipitous discoveries are enabled by scientists who make unexpected observations and then do the work to produce and to contribute the observation as potential evidence to a process of serendipitous discovery. That is, such discoveries are made possible by scientists who express their agency by contributing knowledge to their epistemic community. Marshall and Fleming gain the credit for sagacity *because* they produced potential evidence, *because* Marshall was brash and persistent or not *because* Fleming was sloppy with his petri dishes.

Accounts of serendipity sometimes suggest that serendipitous discoveries make scientific progress through leaps and bounds, by introducing sudden and radical changes to theory or practice (e.g., see Kantorovich, 1998; Meyers, 2007; Morley & de Rond, 2010). In contrast, the tripartite definition of serendipity defended in Chapter 2, the discoveries of *H. pylori* and penicillin described in Chapter 3, and the three methods for fostering serendipity presented in this chapter, suggest that scientific progress by way of serendipity is actually a series of smaller epistemic steps, involving conscientious epistemic action and the (possibly slow) building and support of epistemic agency through trust and confidence.

4.4.b Frameworks of Value

Some issues for consideration arise from the fact that the relevant epistemic community must value the contribution made by the chance observer's insight and actions. First, this is not

only an issue for and in regard to the epistemic agency of the observer herself, but community values also determine what potential evidence will be taken up into a process of discovery. From the perspective of hindsight we could say that *because* the epistemic community *valued* the outcome brought about by a serendipitous discovery—as the medical community valued the curative effects of antibiotics, on ulcers and other ailments, for example—the potential evidence produced from that unexpected observation ultimately resulted in that discovery.

Further, insofar as serendipity presents science with a valued outcome that was unexpected in origin, it represents an increase in value in respect to the original aims of the research processes that were underway at the time. One way to think about serendipity is as unexpected collateral value. Collateral value is attained when an experiment contributes knowledge beyond the aims whose value was used to justify conducting that particular experiment (Kimmelman, 2010, p.93). For example, a study designed to prove the hypothesis that spiral bacteria commonly exists in the stomachs of humans may also demonstrate that the bacteria may cause peptic ulcers, without that hypothesis having been part of the original intentions when the experiment was designed (Marshall, 2006, p.253).[59] Collateral value may arise in addition to the value that justifies the conducting of an experiment, and unexpected collateral value may arise by serendipity in addition to the expected value of an experiment.

But what potential evidence constitutes the collateral value contributed by an experiment must itself be valued by the community. A researcher can maximize the collateral value of an experiment by increasing the overall quantity of quality potential evidence it will

[59] That is, while Marshall was looking for correlations between the bacteria and clinical diagnoses in this study, he (a) did not think he would find anything close to the 100% correlation with ulcers he found in the second stage of this study, and (b) it was widely accepted at that time that the cause of ulcers was already known.

produce. She can do so, for example, by increasing the opportunities for producing potential evidence during an experiment, by supporting the agency of researchers involved in the experiment who could produce potential evidence, and by increasing access by others to any unexpected observations made during the experiment (by following up on these observation in the hope of producing potential evidence that can be made accessible to the community). The means by which collateral value can be maximized are the means by which the probability for serendipity can be maximized within the relevant epistemic community.

In the next chapter, I examine a case taken from contemporary, experimental neurosurgery. The context is clinical research, and the study is an early phase or first-in-human test of an experimental protocol using DBS technology. The guiding value for the relevant epistemic community, then, is ultimately therapeutic value—clinical research ought to be designed to improve the health care of patients. In first-in-human clinical research, for example, because of the uncertainty about the outcome of a protocol that is being tested in humans for the first time, therapeutic value cannot be used to justify asking participants to undergo procedures that are as risky and invasive as neurosurgery. Jonathan Kimmelman develops a framework that he calls translational value as a standard by which to assess the scientific validity and epistemic value of first-in-human clinical research. Using this framework, in the next chapter I look at how first-in-human clinical research can be designed to improve the probability that an unexpected observation will result in a serendipitous discovery by increasing the collateral value of such research for the medical epistemic community.

Chapter 5:
The Case of the Triggered Memory

5.1 Introduction to the Case

The field of experimental deep brain stimulation (DBS) is an appropriate place to look for instances of potential serendipity. As a frontier science in medicine, there remains considerable uncertainty in the field as to what kinds of outcomes can be expected from using DBS in humans. Popularized as an intervention for movement disorders, DBS technology is now being used for a wide variety of psychological and psychiatric conditions. The mechanism of DBS remains unknown, so it is difficult to predict exactly what effects stimulation will have on any individual's brain. Differences between the brains of human participants who are being treated with DBS have resulted, for instance, in the creation of sub-groups of individuals who respond differently to DBS despite sharing a diagnosis (e.g.: Gilbert, 2013). Further, the field is far from consensus on which neural targets are appropriate for stimulation in what conditions. For these reasons, there is a growing number of case reports published from the field of DBS, wherein participants who are being stimulated represent the first-in-human application of this technology at a particular target or to treat a particular condition.

Several of these reports are of singular cases of DBS interventions that led to some unexpected outcome. When the outcome has been portrayed as highly valuable, reports in the media about these cases can resemble "miracle stories" (Racine, Waldman, Palmour, Risse, & Illes, 2007; Schlaepfer & Fins, 2010) I choose one such case report as the focus for my analysis in this and the next chapter—the first case of DBS being provided to an obese participant, whose hypothalamus was stimulated by implanted electrodes in an effort to curb his appetite (Tomycz, Whiting, & Oh, 2012, p. 39).

Notably, it was not the success of this DBS procedure that led to the publication of the case report, but rather the making of an unexpected observation (Gilbert & Ovadia, 2011, p. 2). During the neurosurgical procedure, the stimulation triggered a memory in the participant, who reported having a vivid experience of déjà vu. The observation of the event—which I call the case of the triggered memory—then apparently inspired the team of researchers to embark on a new research direction, hoping to generate an intervention for patients with Alzheimer's disease (AD) (Laxton & Lozano, 2013, p. S28.E2).

As a consequence of the unexpected results of this case, DBS is now being used for the first time to drive the neural activity of the memory circuit, in order to enhance the memories of DBS recipients. Dementia is one of the most debilitating symptoms of a disease estimated to be diagnosed in more than four and a half million new people every year—AD (WHO, 2013). If triggering this participant's memory leads to an intervention for the dementia that comes with AD, then this unexpected observation will have led to a major, valuable, medical discovery.

Such a valuable result, with such an unexpected origin, seems likely to meet the basic criteria I have laid out for serendipity. The chance observation was unexpected in relation to the research being done at the time, and its projected value is great. The insight, actions and agency of the researchers, described in the case report and elsewhere in the media and medical literature, ensured the production of potential evidence that may already be taken up by the community into a process of (probable) serendipitous discovery. Further, features of the relevant epistemic community—the community of contemporary clinical DBS researchers—make the completion of such a process probable. The first part of this chapter describes the case and then establishes that it is indeed a case of potential serendipity.

Second, I address the potential value of the potential evidence produced in response to

the unexpected observation of the triggered memory. The potential evidence about the effects of DBS on memory that is produced by the study described in the case report is, briefly, that "hypothalamic stimulation in this patient modulates limbic activity and improves certain memory functions" (Hamani et al., 2008a, p. 119). The translatability of these results into future research is the standard by which I assess that potential evidence. I look to whether and how the potential evidence about this participant's brain may contribute regulatory value—by contributing directly to an ongoing clinical research program—and whether and how it contributes collateral value to contemporary clinical research. I conclude by raising some further considerations about this case, related to its social and epistemological context—contemporary, experimental, early phase DBS research involving human participants.

5.2 Description of the Case

In the early 2000s, an obese patient was referred to Dr. Andres Lozano and his neurosurgical team at Toronto Western Hospital in the hopes that a new, experimental treatment—DBS—could help him. The participant in this case had been morbidly obese for much of his life. At the time of operation, he was 50 years old and just over 190 kilograms (about 420 pounds). He had already attempted a number of treatment paths, "including dietary regimens, psychological interventions, group therapies, and medications," and was refusing to undergo surgeries to control his weight because he believed they would not prevent him from eating excessively (Hamani et al., 2008a, p. 119). Consequently, he was considered to be treatment-resistant (or "refractory"). Because of the high risks of neurosurgery and the limited predictability of results, it is necessary for most patients who undergo DBS to attempt all other

reasonable treatment options before being referred by their caregivers to neurosurgeons.[60]

Further, as was true for this participant, the health and well-being of patients must be considered to be at greater risk if they continue in the state they are in than if they undergo the risky procedure of implanting DBS technology. In this case, the research ethics board (REB)[61] of the University Health Network (of which Toronto Western Hospital is a member) determined that the particular patient's health was put at greater risk by not attempting to treat his obesity with DBS (despite there being a lack of consensus in the greater medical community about the risks of obesity to people's health). At the time of the REB review, the participant was suffering from a variety of comorbidities related to his obesity, including sleep apnea, diabetes and hypertension. Given the known risks both of DBS and of the participant's current and continuing state of health, Lozano and his team—as well as the REB that approved the obesity-DBS protocol—felt they had good reason to believe the operation was the participant's best treatment option at the time (Hamani et al., 2008a, p. 119). As reported in the literature, : "The basis of the approval for this man was the refractory nature of the obesity, the exhaustion of reasonable therapeutic alternatives, and the possibility of reducing the health risks of chronic obesity should the intervention prove successful" (Hamani et al., 2008a, p. 119).[62]

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[60] I say 'most patients' because there are some categories of disorder, for example, some diagnoses of Parkinson`s Disease, for which DBS is considered the preferred treatment, and patients in these categories do not always have to be treatment-resistant (although they generally do have to be resistant to less risky pharmacological treatment) before being referred for surgery (Williams et al., 2010).

[61] Research ethics board (REB) is a Canadian term; the international or more generic term would be "research ethics committee". Because the case that is the focus of this dissertation is a Canadian one, I use the local term.

[62] Because of the way medical devices are regulated in Canada, the investigating team would have needed REB approval for the use of a human participant in an experimental procedure (i.e., outside of the standard of care for that medical condition), but not for the use of the DBS equipment in a novel procedure; devices are generally approved once for any medical use in Canada, although consent procedures require REB approval for investigational uses insofar as they require an (experimental) operation on a human participant.

5.2.a The Implantation Procedure

DBS is a neurosurgical procedure during which several electrodes on one or more leads are implanted into a participant's brain so that electrical current can be run as a pulse through the electrode contacts to stimulate the neural tissue nearby. In this case, the target within the brain for stimulation was the anterior part of the hypothalamus; the hypothalamus is a region in the 'deep brain', below the thalamus and at the top of the brainstem. The hypothalamus is considered a central neural structure, as many pathways travel through this region to other parts of the brain. It plays a role in regulating such diverse neurological functions as body temperature, drives and motivations related to hunger, thirst and sexual activity, endocrine (hormone-related) functions, emotional behaviour and the nervous system (Diamond, Scheibel, & Elson, 1985, pp. 5–20).

5.2.a.i Reaching the Neural Target

The implantation of electrodes is the most dangerous part of this procedure. Any neurosurgical intervention comes with considerable risk, and this is a lengthy and difficult procedure, for much of which the participant remains awake. Surgeons must first create a working map of the participant's brain and the targeted region. They do this by taking an image of the participant's brain—in this case they used a computed tomographic (CT) scan. A CT scan creates a three-dimensional image of a person's brain by first making X-ray-produced images of 'slices' of the brain that are then processed by a computer. Using images like this helps neurosurgeons determine where the neural target is. Because each human brain is unique, surgeons need to re-establish the location of the neural target in each individual brain by relating images such as CT scans to generic maps of the human brain.

A stereotactic frame is used to ensure that the surgeon reaches the intended target. Stereotactic frames use polar co-ordinates to measure along an arc, so that a three-dimensional grid can be made of the inside of a person's skull. The frame has to be screwed to the skull (with the help of a local anesthetic) to stabilize the co-ordinates before and during the operation. In this way, the measurement obtained previously with the CT scan image can be compared with the physical brain throughout the procedure.

To confirm the correct target has been reached, and before implanting the electrodes that will remain in the brain, a microelectrode is inserted into the targeted path through the surrounding tissue and to the target. This microelectrode stimulates the tissue through which it travels just enough to create a vibration in the surrounding neurons, which in turn can be heard through a speaker in the operating theatre. By the sound of the vibration in the neural cells, experienced technicians can tell where the electrode is located in the brain at that time. The nuclei of the thalamus, for example, make a sound distinct from the nuclei of the hypothalamus.

The hypothalamus is a central region in the deep brain, considered to play a pivotal role in the maintenance of the body's homeostasis. Because of its connection to behaviours such as feeding and drinking, and to functions such as digestion, stimulating it may directly influence subjective sensations of hunger or appetite. Reducing those sensations should, in turn, affect the participant's eating behaviours and consequently physical weight. Thus, the intraoperative testing of the electrode contacts was intended to "identify potential sites to suppress appetite" (Hamani et al., 2008a, p. 119).

5.2.a.ii Design of the Obesity-DBS Protocol

Current evidence suggested there was potential for stimulation to have the desired effect on the participant's appetite and eating habits (Laxton & Lozano, 2013, p. S28.E2). Pre-clinical animal studies demonstrated appetite control via stimulation of the hypothalamus in rodents, dogs and nonhuman primates. The dog and nonhuman primate studies suggested that stimulation of the hypothalamus resulted in delayed feeding, even when the animals were hungrier than normal (Brown, Fessler, Rachlin, & Mullan, 1984; Takaki, Aou, Oomura, Okada, & Hori, 1992). Evidence from other uses of DBS, to treat cluster headache and aggression, suggested that the stimulation of the hypothalamus in humans was relatively safe (Hamani et al., 2008a, p. 119).

Further evidence in favour of stimulating the hypothalamus of this participant was drawn from ("albeit limited") past experiences treating obesity in humans with hypothalamotomy (Hamani et al., 2008a, p. 119). Hypothalamotomy involves 'lesioning'—the destruction of some tissue—of the hypothalamus. When DBS was first popularized, it was on the basis of the assumption that the effects of stimulation were generally the same as the effects of lesioning, also known as ablative therapy. The relevant historical hypothalamotomy cases took place in an era when stimulation was being used only to test for neural targets where tissue may then be destroyed (Quaade, Vaernet, & Larsson, 1974).

In the hypothalamotomy experiment, five obese patients first underwent "electrostimulatory exploration of the lateral hypothalamic area" with the aim that, should a "positive stimulatory response, i.e. hunger sensation" occur, "electrocoagulation[63] of the presumed feeding centre" would then take place (Quaade et al., 1974, p. 112). Two participants

[63] A localized burning of neural tissue with electricity, to create a lesion there.

were given lesions after stimulating their brains led to a "convincing hunger sensation." The researchers determined that the site of the "maximal hunger response"[64] was suitable for a lesion and they used electricity to burn and coagulate the tissue at that site. A third participant was given a lesion three months after the original stimulation exercise.

Postoperatively, the three participants who had lesions, "stated that for the first time they were not very hungry and, especially, felt satiated already during the beginning of their meals" (Quaade et al., 1974, p. 114). This change in sensation resulted in a "significant, but transient" reduction in food intake and consequent weight reduction (Halpern et al., 2008, p. 626; Quaade et al., 1974, p. 116). In the conclusion of the 1974 report, the authors clearly state, "The lesions employed in this series did not produce weight loss in obese humans" (Quaade et al., 1974, p. 116). Nonetheless, this experiment provides additional evidence of the safety of stimulating the hypothalamic region and of the connection between that region and hunger sensations.

Thus, (1) there was reason to believe that the participant may benefit from DBS (in comparison with the risks of staying as he was), (2) there was evidence to suggest the hypothalamus was likely the most appropriate neural target for stimulation to relieve this person of his hunger and to combat his extreme eating behaviour, and (3) there was evidence to suggest that the hypothalamus was a safe target for stimulation. Approval from the institution's REB and consent from the participant were obtained (Hamani et al., 2008a, p. 119). The protocol called for bilateral DBS on either side of the ventral hypothalamus. The primary outcome

[64] This response was of a sensation of hunger: "The hunger reactions may be exemplified by the following utterances, 'I am so hungry that I could eat a whole fried chicken with chips', or, 'I am so hungry that my entire belly feels as a vacuum'." (Quaade et al., 1974, p. 114).

measure for evaluating the success of this obesity-DBS protocol was weight loss observed in the participant (Hamani et al., 2008b, p. 1).

5.2.a.iii Unexpectedly Triggering a Memory

The electrodes implanted in the participant's brain consisted of two leads, one on either side of the ventral (anterior) hypothalamus. Each lead had four contact points at which stimulation could be generated and where the electrodes themselves were found. Precision was required because the target area is small: the hypothalamus is, on average, only .118 to .157 inches thick, and the ventral hypothalamus is only one of at least ten groups of nerve cells (or nuclei) within the hypothalamus. Yet, they are distinct neural regions, with distinct functions. Each of these electrodes, therefore, may have caused a different effect, and so needed to be tested in isolation.

Because stimulation may affect nearby regions of the brain in unpredictable ways, DBS electrodes are tested immediately upon insertion and while the participant is awake, so that side effects can be detected early. The effects of DBS are often (but not always) immediately apparent. For example, when using DBS to treat some movement disorders, such as a severe tremor in a participant's arm, participants and neurosurgeons are generally able to see the tremor stop in the same moment the electrode is turned on, during the procedure.[65] This is both a dramatic and direct confirmation that the desired target has been reached. However, in other movement disorders[66] such as dystonia the effects may be delayed by weeks or even months after the device has been implanted (Talan, 2009, p. 50). One way to avoid harmful side effects

[65] In some cases, the effect of the stimulation is so dramatic and immediate that it can be detected when the microelectrodes are inserted to confirm the target and pathway locations (see previous paragraph).
[66] Of course, this variation between immediate and delayed response is not limited to movement disorders, it has been found to also occur in OCD patients; how great a variation in response may exist in general among disorders treated with DBS is not well known at this time.

is to test the electrodes intraoperatively, before the implantation is permanent.[67] Neurosurgeons conduct a double-blinded test of each contact to ensure it is in the targeted location in the brain and that it does not produce undesirable behavioural, experiential or functional side effects in the participant.

The possibility that unpredictable side effects will occur is generally expected in these procedures. These side effects may be experienced subjectively as well as physiologically. For these reasons, the participant is kept awake for the testing of the electrodes and encouraged to report on any experiences she may be having during the testing period. The participant reports on a fairly constant basis, not knowing which electrodes are turned on or when; the neurosurgeon who receives the reports is blinded by giving the on- off switch to another member of the team to control.[68] Whenever the participant reports an experiential response, the time is recorded and later matched with recordings of the times when each of the electrodes was turned on or off. In this case, "All experiential perceptions were time-locked with stimulation, were specific to the electrode contact and stimulation parameters used, and were obtained at a reproducible current threshold with stimulation performed in a double-blinded manner" (Hamani et al., 2008a, p. 120).

While researchers were testing the first electrode, the participant reported an autobiographical memory whenever the electrode was turned on. He described a detailed and sensory experience of *déjà vu*:

[67] DBS is often touted as a reversible procedure: 'permanence' in this sentence is meant to indicate that another neurosurgical procedure would be necessary to remove them, not that they cannot be removed at all.

[68] Measures are generally taken to ensure neither the surgeon nor the participant can hear when the switch is flipped.

> Unexpectedly, the patient reported sudden sensations that he described as “déjà vu” with stimulation of the first contact tested…He reported the sudden perception of being in a park with friends, a familiar scene to him. He felt he was younger, around 20 years old. He recognized his epoch-appropriate girlfriend among the people. He did not see himself in the scene, but instead was an observer. The scene was in color; people were wearing identifiable clothes and were talking, but he could not decipher what they were saying. As the stimulation intensity was increased from 3.0 to 5.0 volts, he reported that the details in the scene became more vivid. (Hamani et al., 2008a, pp. 119–20)

5.2.a.iv Final Operative Stages

The contact that first triggered the memory was one of the most ventral, or deepest, of the contacts. During the first test, it delivered a 60 microsecond wide pulse of 3.0 volts and 130 hertz (Hamani et al., 2008a, p. 119). Once the memory was reported, the pulse was intensified to 5.0 volts, whereupon the details of the memory experience “became more vivid” (Hamani et al., 2008a, p. 120). The memory experience was reproduced by stimulating contacts 0 and 1 (on the right side of the hypothalamus) and contacts 4 and 5 (on the left side), where contacts 0 and 4 were the deepest and contacts 1 and 5 were more dorsal (nearer to the top of the hypothalamus) (Hamani et al., 2008a, p. 119-20).

Some of the contacts, when tested, produced other side effects. For instance, when the intensity was increased to 5 volts or higher, the participant experienced “an unpleasant generalized warming sensation that was followed by facial hyperemia and sweating” (Hamani et al., 2008a, p. 120). Similarly, a rapid increase in stimulation from none to 5 volts when testing the most ventral contacts created a visual experience of flashes of light that researchers associated with the spread of the current to the optic tracts nearby (Hamani et al., 2008a, p.

120). However, the settings used in the testing phase produced no consistent responses in the participant that related to "his subjective sensation of hunger" (Hamani et al., 2008a, p. 120).

Once the electrodes have been tested, they can be secured to the skull and the neurosurgical procedure completed (the burr hole and wound can be closed). A battery (in this case a 'dual-channel pulse generator') is also implanted under the participant's skin, below the neck, and connected to the electrodes by an insulated wire that travels from the leads, below the skin, and behind the ear. The electrodes are not turned on after testing until the participant is deemed to have fully recovered from the operation.

Even though various intensities have been tested intraoperatively already, the exact pulse width and frequency that will be most effective has to be determined over time—for this task, a DBS programmer is employed. The programmer is trained in titrating stimulation to produce a maximally beneficial effect and minimal side effects. Settings have to be tested over a period of days, weeks or even months and then adjusted; this can be a labor-intensive and lengthy process (Talan, 2009, p. 88). In this case, the first office visit and testing of stimulation effects took place two months after the participant had been discharged from the hospital after surgery (Hamani et al., 2008a, p. 122).

5.2.b The Follow-Up and Results

The obesity-DBS protocol consisted in the neurosurgical procedure described above, as well as continuing care for fifteen months after stimulation was begun (or seventeen months after the DBS implantation procedure took place).

5.2.b.i Results of the Obesity-DBS Protocol

The original settings for stimulation had no effect on the participant's weight. For the first six months (beginning two months after the surgery), stimulation was set to a high

frequency (130 Hertz).[69] Because there was no indication in the intraoperative testing phase that one site or contact was implicated for the suppression of appetite over any other, the electrodes were used as homologous pairs. Two electrodes, one on each lead, in similar positions in relation to the other electrodes and to the hypothalamus (0,4; 1,5; 2,6; and 3,7), worked together to produce a current through the hypothalamus (one acting as a positive and the other as a negative node) (Hamani et al., 2008b, p. 1).

After six months with no change in weight or eating behaviour, the stimulation parameters were altered. In other cases of DBS for other conditions, changes in stimulation frequency have had an effect on clinical benefit (Hamani et al., 2008b, p. 1). A lower frequency (of 50 Hertz, 3-4 Volts and a pulse width of 210 microseconds) was therefore used for the following five months. During this five months, the participant lost 12 kilograms (26.4 pounds) of weight. He did not change his eating habits or exercise more frequently, but rather reported "reduced food cravings and a decreased tendency to binge" while the stimulation was turned on at that setting (Hamani et al., 2008b, p. 1).

However, this weight loss did not last through the final four months of the fifteen month stimulation protocol. The participant had been given a hand-held controller for his DBS device, allowing him to turn the stimulation off,[70] which he began to do some evenings, "because he had a desire to eat and he felt it might help him sleep" (Hamani et al., 2008b, p. 1). While the stimulation was off, the participant returned to his past eating behaviour of nighttime binging.

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[69] Details about voltage and pulse width for this time period are not given in the case report or supplementary materials.

[70] This is standard procedure for many DBS applications, normally for reasons of safety. (Personal communication, Nir Lipsman, March 2015). A patient with a DBS implant, for example, cannot pass through airport security devices with the stimulation turned on. There is no comment in the case report or subsequent literature about this feature of the protocol, and so I have no reason to believe it is not accepted by the community as standard procedure for like cases.

By the end of fifteen months of stimulation he had regained what he had lost and weighed a total of 192 kilograms (just over 423 pounds). Thus, the original goal of the procedure was only partially met. DBS stimulation of the hypothalamus of an obese patient was shown to be safe, but data about efficacy—whether the long-term appetite suppression could be obtained—was inconclusive.[71]

In the review literature on DBS for obesity, the case published by Hamani and colleagues (Lozano's neurosurgical team) is often mentioned but rarely considered as having contributed any valuable evidence to a process of discovery in obesity medicine (e.g.: Melega, Lacan, Gorgulho, Behnke, & De Salles, 2012, pp. 6–7; Pisapia et al., 2013, p. 38) For example, consider the following quotation:

> The first foray into DBS for obesity was reported by Hamani et al. in 2008. A 50-year-old morbidly obese man underwent implantation of bilateral ventral hypothalamic DBS electrodes. Although he did report a decreased appetite when the stimulator was turned on, the most striking finding was that stimulation elicited the sensation of déjà vu and improved memory recollection; this phenomenon of memory enhancement was attributed to stimulation of the nearby fornix. Since this time, DBS of the hypothalamus has been primarily applied to treat chronic cluster headache.
>
> (Tomycz et al., 2012, p. 39)

5.2.b.ii Research Conducted in Response to the Triggered Memory, and Results

As Lozano later suggests in a co-authored review of the case of the triggered memory, in response to the unexpected intraoperative observation, "[n]umerous additional measures were

[71] Inconclusive mostly because, in this singular case, the participant interrupted the stimulation before conclusions about its effects on his obesity could be drawn with any certainty.

obtained" (Laxton & Lozano, 2013, p. S28.E2). These measures were obtained in order to confirm the inference that the memory was being triggered by the effects of stimulation on a particular neural region. The procedures needed to take such measures in some cases coincided with the obesity-DBS protocol, but also included amendments and additions to that protocol. These included: memory-related psychological tests; confirmation of the location of the electrode with further imaging; and producing images of neural activity to confirm that the stimulation was "driving" neural activity at a particular site (Hamani et al., 2008a, 2008b; Laxton & Lozano, 2013, p. S28.E2).

Several aspects of the protocol reported in 2008 were needed to produce evidence of a causal connection between stimulation and enhancement of the participant's memory. First, the double-blinding and time-stamping procedures used in the intraoperative testing phase allowed consistent correlations to be drawn between the triggering of the memory and the activation of a stimulating current, as well as between the vividness of the memory and the intensity of the stimulation. Further, images taken of the participant's brain postoperatively were used to confirm the placement of the electrodes in the brain. It was shown that the electrodes most strongly associated with the triggering of the memory were positioned quite near to the fornix, a major fiber pathway that travels beside the hypothalamus and interconnects the nearby hippocampus with other regions of the brain, significantly related to the memory circuit (Hamani et al., 2008a, p. 120; Laxton & Lozano, 2013, p. S28.E2).

In the first postoperative follow-up office visit two months after the implantation surgery, the electrode contacts were tested one at a time again, and the experiential effects were found to be reproducible. The participant reported the same déjà vu experience as each contact was tested, and similar results of increased vividness (in the detail of the memory and in the intensity of the memory experience) when the stimulation frequency was increased. As well,

other side effects (the feeling of warmth, flushed face and sweating) were reproduced when the frequency was increased rapidly (Hamani et al., 2008a, p. 122).

During the months of post-operative follow-up visits, several more tests were done to further characterize the aspects (or kinds) of memory that seemed to be enhanced by stimulation. It is typical in any DBS procedure to conduct a comprehensive psychological assessment using standardized tests both before and after the implantation of the device.[72] In this case, tests were done at baseline (before the surgery) and after three weeks of chronic stimulation (Hamani et al., 2008a, pp. 120–21). The researchers then used a Reliable Change Index (RCI) to compare the changes in test results observed in this participant with averages obtained from a healthy control group (Hamani et al., 2008b, pp. 3–4, 8 & 9). Of the neuropsychological measures taken via standardized tests, two showed significant improvement: the California Verbal Learning Test and the Spatial Associative Learning Test. For the researchers, the specificity of these improvements was significant: "The lack of global improvements across the various tests speaks against a nonspecific enhancement in memory as a consequence of practice, learning, or increased attention or motivation with stimulation" (Hamani et al., 2008a, p. 122). In other words, stimulation was not causing general improvements, but rather specific ones, and therefore a causal connection between stimulation at that site and particular kinds of memory improvement could be inferred.

Further tests characterized the kinds of memory being improved. Two separate tasks were used to test the participant's recollection abilities. The first series of tests required the participant to decide which one of a pair of words (from a total of 80 pairs) was more pleasing.

[72] This precaution is the result of considerable experience in the field with unanticipated, psychological side effects. The tests are done to ensure that any changes in the participant's psychological profile are detected.

Ten minutes later he underwent a recognition test with a new set of word pairs, to see how often he was aware when test pairs were the same (both words were repeated), recombined (two words from the previous set were combined in a different pairing) or where a new word had been introduced together with one word from the previous set. The participant was further asked to indicate a response of either "remember" or "know" to describe his decision about each word pair. "Remember" signified that he could recall the original context in which the words had been presented to him, and "know" signified that he could not recall that context but the pairing was nonetheless familiar to him (Hamani et al., 2008a, p. 121). This test was repeated one week later. Although double-blinded at the time, the report states that stimulation was randomized to *off* for the first occasion and to *on* for the second. The participant provided a "remember" response much less often when the stimulation was *off* (only 43% of the time) than when the stimulation was *on* (70%) (Hamani et al., 2008a, p. 122).

The second test series was similar, but used different word lists and recognition tasks. Again, any changes in results were compared to estimates provided by an RCI. This second test was administered a year after stimulation began, this time with the *on* and *off* stimulation conditions being tested in the same day, and within an hour of one another. The series began by presenting the participant with 120 word pairs and asking him to construct a sentence aloud that meaningfully used the two words in each pair. Then, a test for "associative recognition" asked the participant to positively respond when pairs presented to him were either intact or had been recombined. A second test studied familiarity by asking him to respond positively only to intact pairs. Positive responses to recombined pairs in this second part of the test suggested familiarity with the pair but a lack of recollection of the original context in which they had been presented to him. The results of these tests were combined with results from the first series of

tests to measure the difference between improvements in recollection and improvements in familiarity (Hamani et al., 2008a, p. 121).

Finally, the researchers took functional images of the participant's brain, to show how stimulation was affecting his neural activity. This final procedure was meant "[t]o assess whether hypothalamic stimulation was driving hippocampal activity" (Hamani et al., 2008a, p. 123). When the stimulation was turned *on* in a single electrode, on either the right or the left side, "a significant increase in the activity" in the relevant neural regions was observed (p.123).[73] This result was considered possible evidence for the hypothesis that stimulation near the fornix was driving (or increasing) the activity of neural regions that make up the memory circuit through the hippocampus. This hypothesis was reported as further affirmed by the results of the memory tests described above, which seemed to point to improved function in types of memory that are known to be related to the hippocampal region in which the increased activity was being observed.

5.2.b.iii The Obesity-DBS Protocol, as Amended

It is difficult to separate out what parts of the protocol as reported were additions or amendments to the original obesity-DBS protocol in response to the intraoperative observation of the triggered memory. The case report does not do this work for the reader, nor does it specifically mention whether the specific additions and/or amendments to the original, approved protocol were subject to REB review.[74] However, it remains a fact that

[73] The relevant neural regions were, specifically, the "ipsilateral mesial temporal lobe structure, mainly the hippocampus and parahippocampal gyrus region" (Hamani et al., 2008a, p. 123).

[74] Because no such details are given in the case report, I resist speculating about them here. This is not to suggest that REB approval was not sought for the amendments, nor that consent for the amendments was not obtained from the participant, but only to note that the case report does not clarify how the REB process did or did not accommodate the changes that were made. I requested a copy of the original documents; my request was refused for reasons of privacy.

the study as described in the 2008 report was different than the study that presumably would originally have been designed and approved for the obese participant. I explore the implications of this difference in Chapter 6.

For the purposes of this and the following chapters, to express clearly when I am discussing the protocol described and reported in the 2008 published case report, from this point forward I will refer to it as "the obesity-DBS protocol *as amended,*" which is short-hand for, "the obesity-DBS protocol *as amended in response to the intraoperative observation of a triggered memory, in order to confirm the correlation of a particular kind of memory response with specific stimulation parameters and neural location, in the obesity-DBS participant.*"

5.2.c Publication of the Case Report

The 2008 publication focuses on the unexpected observation of the triggered memory and the memory-related results from the obesity-DBS protocol *as amended* that took place in 2003. As published, "This report emphasizes the effect of hypothalamic stimulation on memory function. The outcome with respect to appetite and obesity is available in the supplementary materials" (Hamani et al., 2008a, p. 122) The design of the original protocol was for stimulation of the hypothalamus because it was intended to influence sensations of hunger and appetite of the participant. However, most of the details about those aspects of the procedure are relegated to the supplementary materials. The focus of the case report, rather, is specifically on the memory-related results. It is important to note that, unlike case studies of incidental findings that occur during clinical research or medical practice, this report described a new protocol that had been initiated in response to an unexpected observation.

5.2.c.i Potential Evidence Produced in Regard to Memory and DBS

The authors of the case report conclude that while stimulation seemed to improve the

participant's ability to recollect the word pairs, it did not have a significant effect on the familiarity of the word pairs to the participant. Thus, the experiments done indicate that stimulation was having a specific effect on particular aspects of memory related to recollection; the effects of stimulation were not global, but were specific (Hamani et al., 2008a, p. 123). The improvements in the participant's test scores were probably not due to global improvements in his emotional state, attention or motivational states caused by the stimulation. Rather, the stimulation was inferred to be causing specific improvements in particular memory functions.

The inference that the unexpected intraoperative observation indicated a causal relationship was reinforced by the fact that the particular memory functions affected were those already known to be associated with the hippocampus. As the case report suggests, the tests were chosen on this basis: they are described as "recognition tasks with high sensitivity and specificity for hippocampus-dependent retrieval processes" (Hamani et al., 2008a, p. 121). The hypothesis being tested was two-fold: first that the triggered memory revealed a causal connection between memory function and stimulation in that region, and second that this causal connection related to known theory and data on memory function and particular neural regions, specifically parts of the memory circuit associated with the fornix. Consequently, the potential evidence in regard to memory and DBS that was produced by this research is evidence that "hypothalamic stimulation [near the fornix] in this patient modulates limbic activity and improves certain memory functions" (Hamani et al., 2008a, p. 119).

5.2.c.ii An Unexpected, Novel Direction for DBS Research

The 2008 case report has been cited often in the media and in the DBS literature[75], mostly in reference to the potential value of the unexpected observation of the triggered memory. In particular, the case is supposed to have played a principal role in initiating a

[75] Google scholar, as of September 2015, calculated 249 different citations of the article in total.

program of research into the potential therapeutic benefits that DBS may bring to sufferers of AD. An explicit connection between the memory observation reported and the potential for DBS to treat the loss of memory function in people with AD has been repeatedly made in the literature, by the authors of the case report, by their colleagues in the field, and by the popular science media (e.g.: Black, 2012; Hurley, 2008; Laxton & Lozano, 2013; Lykestsos, Targum, Pendergrass, & Lozano, 2012). That is, the potential evidence produced by the obesity-DBS protocol *as amended* has been projected to be (potentially) veridical evidence for the following hypothesis: "that stimulation in the fornix/hypothalamus could alter activity in medial temporal memory circuits, thereby providing a safe and potentially beneficial effect on memory in 6 patients with early AD" (Laxton et al., 2010, pp. 522–533).

The basic inference that DBS can drive the memory functions of the brain and the subsequent investigation of DBS as a therapeutic option for AD are a novel inference and intervention. Previous data had indicated that stimulation had an inhibitory, rather than enhancing, effect on memory (Suthana et al., 2012). With DBS for Parkinson's related movement disorders, it had been previously observed that while improving the motor symptoms of PD, DBS tended to further impair the already afflicted spatial working memory of patients (Hershey et al., 2008). As well, lesions in the area of the fornix in both animals and humans had caused memory deficits in experiments past (Laxton et al., 2010, p. 522). The idea that stimulation could *enhance* memory instead was novel.

As well, this case presents new and dramatic evidence for the hypothesis that DBS may restore neural functions over time. Dominant theory in the field of DBS even today is that the effects of stimulation mimic the effects of lesions. Despite considerable speculation, the mechanism by which DBS modulates neural activity remains a mystery (Ineichen, Glannon, Temel, Baumann, & Surucu, 2014; Kringelbach, Jenkinson, Owen, & Aziz, 2007; Lozano &

Lipsman, 2013, p. 416). However, the possibility that stimulation could drive activity in neural circuits and possibly even lead to the generation of new neurons to replace those lost to disease—i.e.: neurogenesis—is being proposed in light of recent preclinical research that Lozano took up following the case of the triggered memory (Encinas, Hamani, Lozano, & Enikolopov, 2011; Laxton & Lozano, 2013; Stone et al., 2011). If confirmed in humans, this new insight into the effects of DBS suggests that alternative theories about the mechanism of DBS are still needed and, correspondingly, new ways to use DBS might be possible. Thus, in a very real sense, the production of potential evidence about memory and DBS through the obesity-DBS protocol *as amended* led to a new direction for DBS research.

5.3 The Case as *Potential* Serendipity

> A … study serendipitously showed that bilateral deep-brain stimulation in the hypothalamus to suppress appetite in a morbidly obese subject evoked vivid autobiographical memory and improved performance on paired-associate word learning, leading to the inference that the memory enhancement was due to current spread to the nearby fornix (a major hippocampal projection pathway). These findings emboldened the authors to conduct an unblended trial of continuous deep-brain stimulation in six persons with Alzheimer's disease over the course of 1 year. The procedure proved to be relatively safe and appeared *to* slow cognitive decline, albeit insignificantly. However, standardized low-resolution electromagnetic tomography and F-flourodeoxy-glucose-positron-emission tomography showed restoration of more normal corticolimbic connectivity, supporting the idea that deep-brain stimulation near the fornix *may* enhance memory. (Black, 2012, p. 564)

As the quotation above suggests, this case of the triggered memory may indeed include all three of the elements necessary for serendipity—chance, sagacity and a valued outcome (currently projected). The key observation was *unexpected*: even if the researchers were unsurprised to see a memory-related response in their participant when stimulating the hypothalamus, the enhancement effect was indeed both a surprise and an unintended consequence of the experiment's design. The triggered memory presented an anomaly that inspired the *sagacity* of the researchers, who were "emboldened" to investigate further. They made a connection between what they already knew about the hypothalamus and memory and what the participant reported about his memory experience. This connection had the potential to change as well as extend theory about the mechanism of DBS and how the brain works—it was a strategic, and meaningful connection. Further, the potential evidence produced by the obesity-DBS protocol *as amended* has potential *value* as evidence for a therapeutic hypothesis and thereby may contribute to a process of medical discovery. However, in 2013, a review of the literature concluded, "it is still premature to conclude that DBS can be used in the treatment of AD, and the field will wait for the results of ongoing clinical trials" (Hescham, Lim, Jahanshahi, Blokland, & Temel, 2013). The results of the triggered memory study represent potential, if not veridical, evidence for a projected, potentially valued discovery.

Further, conditions in the relevant context and features of the relevant epistemic community suggest there is a high probability this unexpected observation of a triggered memory will (in time) come to fruition in the completion of a process of serendipitous discovery. The social and epistemological context of this case, that is, is conducive to fostering serendipitous discovery. First, the field of neurosurgery and DBS accepts that valuable discoveries often arise unexpectedly: for example, the very first use of DBS as a replacement for ablative techniques is considered "serendipitous" (Benabid & Torres, 2012). Second, the agency

of the Toronto team is supported by their epistemic community. Lozano himself is a recognized authority in the field who has been associated with innovative practices in DBS in the past—most notably, for his work on DBS as an intervention for depression (e.g., Glannon, 2008, pp. 325–6).

In a recent TED talk on innovative research in January of 2013, Lozano touches on his research with depression and on research currently underway in DBS for AD. In particular, he suggests, "in Alzheimer's disease, the lights are out, but there is someone home, and we're able to turn the power back on to these areas of the brain, and as we do so, we expect that their functions will return."[76] While he does not mention the observation of the triggered memory or the obesity-DBS participant in the TED talk, this does demonstrate the positivity with which the new research direction has been taken on. Lozano and many members of his team are recognized and trusted agents within their epistemic community. They inspire the confidence of their colleagues, even among those who disagree with their conclusions about why the obesity-DBS protocol *as amended* is important (e.g.: Suthana et al., 2012). It is probable that the research they propose will be funded (demonstrated by the fact that Phase II trials for AD-DBS are currently underway), and that colleagues in other institutions will put the potential evidence they produce to use as evidence for their own hypotheses.

Finally, the publication of the case report in 2008 ensured that the potential evidence produced by the obesity-DBS protocol *as amended* is disseminated to colleagues in the broader epistemic community. The sharing of this knowledge means that it is more likely that, if it becomes useful as a solution to a problem, the researchers who need this knowledge will find it. The case report has already been taken up or cited by other researchers: as negative results for

[76] Retrieved May 2014, from http://www.ted.com/talks/andres_lozano_parkinson_s_depression_and_the_switch_that_might_turn_them_off

hypothalamic obesity-DBS, as potential evidence for a hypothesis about AD, and as potential evidence for the ability of DBS to drive neural activity. Thus there are multiple paths that may be taken in a discovery process that, when a valued outcome is determined, could be a process of serendipitous discovery tracing its origins to the case of the triggered memory with the obesity-DBS protocol *as amended*. For all of the above reasons, the 2008 case report describes a case of potential serendipity.

5.4 Assessing the Value of the Potential Evidence Produced

As I argued at the end of Chapter 4, only evidence that is in a form and has content that the relevant community values will be taken up into a process of serendipitous discovery. For instance, the community of scientists will only take up potential evidence that is scientifically valid and useful in relation to scientific hypotheses. The community of clinical researchers will only take up the potential evidence produced by the obesity-DBS protocol *as amended* if it contributes something of value to clinical knowledge and the processes of clinical research.

The question to ask, then, is what might the memory-related results of the obesity-DBS protocol *as amended* be evidence *for*? I explore four possibilities in the following section, that can be roughly grouped together under two kinds of value that the potential evidence may contribute to clinical research—regulatory value and collateral value. Regulatory value results from a direct contribution that evidence makes to a particular research process in clinical research; collateral value results from the indirect contributions that evidence may make to the broader community of clinical researchers and medicine.

First, the memory-related potential evidence produced by the obesity-DBS protocol *as amended* may contribute regulatory value, by contributing directly to the progress of clinical

research. It may contribute evidence for a refinement of the obesity-DBS protocol in future obesity-DBS research. Or, the potential evidence may lead to a new study in other participants with DBS implants in the same region of the brain to test the hypothesis formed in response to observing the triggered memory in the original, obese participant. As my analysis will show, the potential evidence could contribute regulatory value by initiating a new research program investigating memory and DBS.

Second, the memory-related potential evidence produced by the obesity-DBS protocol *as amended* may contribute collateral value by informing other loosely related areas of clinical research. For example, the potential evidence may lead to new research in a different target population with memory disorders (for example, the current AD-DBS research) testing the hypothesis formed in response to observing the triggered memory. Or the potential evidence may lead to some as-yet undetermined hypothesis in neuroscience or medicine.

Recall from earlier chapters that the projected value that causes an observer to pay attention to and follow up on an unexpected observation does not necessarily have the same content as the valued outcome that (ultimately) grants that unexpected observation the status of serendipity. It may be that some valued outcome *unimagined* by that observer at that time will be a serendipitous discovery.[77] At the point in the process when the valued outcome of the unexpected observation remains undetermined, we can only assess the potential evidence in relation to the likelihood that it will contribute to valued outcomes currently projected. The standard by which I assess the probability of this potential evidence contributing to each projected outcome uses a concept introduced by Kimmelman—the concept of "translational distance."

[77] It is not impossible for the same unexpected observation to result in more than one serendipitous discovery.

What determines whether the potential evidence produced by the obesity-DBS protocol *as amended* makes a valuable contribution to medicine (by extending or changing theory) is how well it abides by the principle of minimal translational distance. Kimmelman defines the principle in terms of seeking "to minimize the number and extravagance of assumptions in launching human studies" (Kimmelman, 2010, p. 118). Reviewers of proposed first-in-human clinical trials should consider the translational distance between the evidence being used to justify conducting a trial and the inference being made about how that evidence will play out in human participants.

Kimmelman focuses on the use of preclinical animal research being used to justify predictions that some interventions will be effective in humans. In many cases, there is considerable translational distance between the animal model and the human disease that constrains predictions about how an intervention that has proven effective in that animal model will work in humans (Kimmelman, 2010, p. 118). In contrast, there should be minimal translational distance between the potential evidence generated by research with those animal models and the proposed application of that evidence to human participants. Otherwise, inferences made about what risks the proposed application poses to research participants as well as what benefits they may receive from participating cannot be used to justify conducting that research with those participants. Instead, Kimmelman recommends taking small steps in early phase research, beginning with first-in-human trials designed to minimize that translational distance, before embarking on "bold studies that aim to show safety and substantial biological response in a single shot" (Kimmelman, 2010, p. 118).

In regard to the case of the triggered memory, the relevant judgment is whether there is minimal translational distance between the observations made during the obesity-DBS protocol *as amended* with the obese participant and hypotheses proposed for testing by additional

clinical research with other participants. That is, is the distance between the obese participant and the new research participants minimal enough to translate evidence from the obesity-DBS protocol *as amended* into a new research program, as evidence for a hypothesis there? The potential evidence being assessed—the results of the obesity-DBS protocol *as amended*—was summarized by the authors of the case report as follows: "hypothalamic stimulation in this [obese participant] modulates limbic activity and improves certain memory functions" (Hamani et al., 2008a, p. 119). The relevant translational distance is between the observations made of this single participant to the inference that research with other human participants is warranted, on the basis that those observations are potential evidence for the hypothesis being tested in those new participants.

5.4.a Regulatory Value and Collateral Value

Minimal translational distance is achieved, for example, when the results of one clinical study directly inform the design of another study that follows it. Kimmelman defines regulatory value as the value of a clinical study in terms of its contribution to the same research process. An example of this would be the completion of one phase in a four-phase research program that enables the next step in the research program (Kimmelman, 2010, pp. 91–92). One of the aims of early clinical trials with human participants is to test the parameters of a protocol's design. For example, Phase I clinical research tests the safety of proposed interventions in humans; Phase II clinical research typically aims to establish the parameters for efficacy by adding controls designed to produce generalizable results. In contemporary clinical research such as the obesity-DBS protocol, the safety and efficacy goals are collapsed into a single study. The potential evidence produced by the obesity-DBS protocol *as amended* has regulatory value insofar as the finding—that hypothalamic DBS is both safe and has a predictable memory-related outcome—can be used to justify further clinical research.

In addition, the potential evidence produced by the obesity-DBS protocol *as amended* contributes collateral value to the epistemic community of clinical DBS researchers. As reported by the authors of the 2008 case report, "[t]he effects of hypothalamic stimulation on memory shown represent an unanticipated *collateral* effect in the context of a putative treatment for morbid obesity" (Hamani et al., 2008a, p. 123, emphasis mine). Recall that collateral value reflects the contributions made by "informing other areas of loosely related research practice" (Kimmelman, 2010, p.93). The potential evidence produced by the obesity-DBS protocol *as amended* may, eventually or indirectly, lead to a major discovery in AD intervention; contribute important insight into how the brain works; and change the way people think about how DBS works to modulate neural activity. As such, the potential evidence could change current theory in one or more important ways that are only indirectly related to the original aims of the obesity-DBS protocol or the additional epistemic aims of the obesity-DBS protocol *as amended* in response to the observation of the triggered memory.

I will now look more specifically at the ways in which the potential evidence produced in response to the observation of the triggered memory could contribute either regulatory or collateral value—or both—to the processes of clinical research.

5.4.a.i As a Contribution to Obesity-DBS Research

The case report and supplementary materials published in 2008 contributed limited results to the field of obesity-DBS research. As a test of the safety of implanting DBS technology and stimulating at the hypothalamus, the results were positive. The same cannot be said with respect to the results about efficacy. Given the lack of conclusive results about efficacy, further research is needed to demonstrate if stimulating the hypothalamus, although safe, will sufficiently benefit those who undertake the risks of the invasive implantation procedure. Thus,

the obesity-DBS results from this case contributed limited data on safety—an addition of one case—and no new information about efficacy. It follows that the obesity-DBS protocol contributed some, but not very much, regulatory value to the processes of obesity research.

Meanwhile, the obesity-DBS protocol *as amended*, which aimed to generate knowledge about memory and not obesity, contributed no additional data to obesity research, and thus has neither regulatory nor collateral value in respect to the processes of obesity research.

5.4.a.ii As a Contribution to Memory-DBS Research

Notable about the way in which the 2008 publication reports the memory results of the obesity-DBS protocol *as amended* is that it includes specific reference to the obese participant. Recall: "hypothalamic stimulation [near the fornix] *in this patient* modulates limbic activity and improves certain memory functions" (Hamani et al., 2008a, p. 119, emphasis added). The authors are cautious to assert that the results of the obesity-DBS protocol *as amended* are specific to the obesity-DBS participant. Their caution suggests that, until further research is done with other participants, it remains uncertain to what degree the results of this study might be replicated in other humans, including humans with potentially significantly different brains—like the brains of people with dementia or other memory-disorders.

Two of the participants in the AD-DBS trial that followed the obesity-DBS study had similar déjà vu experiences during intraoperative stimulation (Laxton et al., 2010, p. 524). The fact that the experience of déjà vu was replicated in these participants suggests that the results from the obesity-DBS protocol *as amended* are generalizable. However, the participants in whom the results were replicated were different from the obese participant in potentially significant ways—for instance, the obese participant had a normal functioning brain in respect to memory, but the AD-diagnosed participants were experiencing the early stages of

neurodegeneration and consequently symptoms of memory loss. No previous research or controls were used to establish how this difference between a normal and a diseased brain might or might not have influenced the results of stimulation. In order to minimize the translational distance between the obese participant's brain and the AD-diagnosed participants' brains, further research to confirm the generalizability of the results from the obesity-DBS protocol *as amended* in other participants with normal brains (in respect to memory) could be done. Evidence about the obese participant's triggered and enhanced memory and its relationship to the stimulation of his hypothalamus could be potential evidence for a generalizability hypothesis, and thereby for the design of an early phase clinical trial with other participants with normal brains (in respect to memory), contributing regulatory value to clinical research.

The potential evidence generated by the obesity-DBS protocol *as amended* is likely to also contribute collateral value by contributing to an ongoing research program about memory and DBS. Recall that collateral value is an evaluation of the contributions research makes "by informing other areas of loosely related research practice" (Kimmelman, 2010, p. 93). Well-designed research on memory and DBS could use various parameters to test the impact of stimulation on the memory circuits of DBS recipients, obtaining valid results that could contribute to potentially multiple other hypotheses.

For instance, the effects of stimulation on memory may be different depending on where, when, and for how long the stimulation is applied. Researchers who are testing the effects of stimulating the entorhinal cortex suggest that it is a better location in the memory circuit from which to drive activity with electrical stimulation. They further claim that electrical stimulation of that region enhances spatial memory, for example, in particular when the stimulation is applied while participants are learning new locations (Suthana et al., 2012). As

well, stimulation at different points in the memory circuit may produce different—possibly more valuable—functional results in populations with dementia. In addition to the entorhinal cortex, researchers have tested for memory effects in human participants with DBS located at the nucleus basilis of Maynert and are now testing for memory effects in participants by implanting DBS technology in the frontal lobe. There is evidence for each of these targets to suggest it may be as or more appropriate a location for stimulation than the fornix to achieve the hoped-for therapeutic effects in AD-diagnosed participants (Hescham et al., 2013; Laxton & Lozano, 2013; Neergaard, 2013).

In sum, using the potential evidence produced by the obesity-DBS protocol *as amended* to justify further research into the relationship between memory functions and DBS with the aim to produce generalizable knowledge would have both regulatory and collateral value. Such clinical research on memory and DBS could minimize the translational distance between the obese participant and participants with dementia by producing further evidence about the best way to use stimulation to drive activity in the memory circuit, and about the best location for stimulation in participants diagnosed with dementia.

5.4.a.iii As a Contribution to Alzheimer's Research

Members of the Toronto DBS research team have explicitly claimed there is a direct link between the obesity-DBS protocol *as amended* and the AD-DBS research program. Indeed they report that the obesity-DBS protocol *as amended* in response to the observation of the triggered memory was the "sentinel" case for the AD-DBS trial. They thereby assert that the potential evidence had regulatory value in respect to the AD-DBS trial. However, when the translational distance between the potential evidence produced by the obesity-DBS protocol *as amended* is

taken into account, questions can be raised in particular about the presumed regulatory value of that potential evidence in relation to the AD-DBS trial.

First, the case of the triggered memory is just that, a single case. It may also be a significantly different kind of case, raising questions as to whether the obesity-DBS protocol *as amended* could have produced potential evidence for any particular hypothesis guiding the design of the AD trials. For one, the obese participant had an apparently normal brain beyond his problems with appetite control, and the AD-DBS participants are experiencing memory loss and neurodegeneration. This difference means, for some, that "You can't apply [the inferences made about the triggered memory] to Alzheimer Disease. That's a reach" (Daniel Tarsy MD, quoted in Hurley, 2008, p. 11). Further, the participant in this case was stimulated near the fornix. But the neurodegeneration of the memory circuits that leads to memory loss in AD patients begins at the entorhinal cortex: there is reason to believe that if DBS can indeed help improve or slow the loss of memory function in AD patients, stimulation may be best applied sooner and in a different location than the fornix (Black, 2012, p. 564). Further research still has to be done to ascertain which neural target and DBS protocol may work best for future AD patients (Hescham et al., 2013).

Second, recall the Phase I AD-DBS trial tested the hypothesis, "that stimulation in the fornix/hypothalamus could alter activity in medial temporal memory circuits, thereby providing a safe and potentially beneficial effect on memory in 6 patients with early AD" (Laxton et al., 2010, pp. 522–533). This hypothesis was formed on the basis of one case, the case of the triggered memory, and was first tested for generalizability in the AD-DBS Phase I trial. The Phase I AD trial showed that stimulation near the fornix was safe in AD-diagnosed participants, and further suggested that the hypothesis regarding the causal connection between stimulation and neural activity in the memory circuit could be correct. Two of the patients in this trial

experienced déjà vu during the implantation procedure, in a fashion similar to the original obese participant, and follow-up testing suggested that some of the AD participants' rate of cognitive decline may have been slowed, in relation to a baseline drawn from AD data (Laxton et al., 2010, pp. 524, 526).[78] However, the effects on memory functions have been insignificant and inconclusive, despite biological evidence of improved neural activity (Black, 2012; Laxton et al., 2010).[79] In any case, these results (both positive and negative) cannot post hoc justify conducting the research that produced them. To assess regulatory value, however, a more important question than whether the research is producing valuable clinical results is the question of whether the results of the obesity-DBS protocol *as amended* were potential evidence for the hypothesis being tested by the Phase I AD-DBS trial.

Was the generalizability of the potential evidence contributed by the obesity-DBS protocol *as amended* justifiably tested in a new group of research participants with AD diagnoses? It was clear to researchers involved in the AD-DBS trial that further evidence was needed to justify the design and implementation of the AD-DBS protocol in AD-diagnosed participants (Laxton & Lozano, 2013; Laxton et al., 2010; Lykestsos et al., 2012). To explain why they think DBS may benefit AD-diagnosed participants, the authors of the first report on the Phase I AD-DBS trial (Laxton et al., 2010) call upon a variety of additional evidence, including theoretical approaches to AD that suggest driving neural systems with stimulation may be therapeutic, and neuroscientific approaches to the brain that affirm the therapeutic inference

[78] "A phase 2, multi-centre trial is now [in 2013] underway in which 50 Alzheimer's patients will have electrodes implanted in their brains, but only half will have the stimulation turned on immediately. In the others, it will be turned on in a delayed fashion. This will allow Lozano and his research collaborators to compare and contrast the results in memory performance and brain structure." Retrieved February 2015 from: http://www.research.utoronto.ca/edge/winter2013/deep-brain-stimulation/#sthash.2Jg2sgDi.dpuf

[79] That is, in the report on the phase 1 AD-DBS trial, investigators report that when compared to the estimated normal rate of degeneration in AD patients, two of the participants in the trial exhibited a slower rate of decline. The trial thus used historical controls and their sample size for efficacy was small (Laxton et al., 2010).

(p. 522). This additional evidence was needed to support the presumption that the translational distance between the obese participant and the AD-diagnosed participants was sufficiently minimal to use results from clinical research with that single participant to justify research with the new group of potential participants.

However, evidence about AD does not necessarily justify DBS of the fornix (Hescham et al., 2013; Laxton & Lozano, 2013). The only obvious evidence available to the AD-DBS researchers when they designed their trial that the fornix is an appropriate target from which to drive neural activity in the memory circuit was the potential evidence produced by the obesity-DBS protocol *as amended.* If the obesity-DBS protocol *as amended* was indeed the pattern after which the AD-DBS trial was designed, then whether the translational distance was sufficiently minimal between those cases would have been an important question for the research ethics board that reviewed and approved the AD-DBS trial. I have raised questions above that suggest the translational distance was not minimal. Further research to demonstrate the generalizability of the results from the obesity-DBS protocol *as amended* could have closed the distance sufficiently to warrant research with a group as distinct from the obese participant as the AD-diagnosed participants.[80]

A related issue arises from the fact that even though similar memory-related results were seen in some of the AD-DBS participants this does not, ad hoc, justify conducting research with those participants. While questions of ethics have been reserved for Chapter 6, here it is perhaps important to note the circularity of an argument: the (potential) generalizability of the results from the obesity-DBS protocol *as amended* was part of the justification for implanting the AD participants with DBS technology. The need to demonstrate that generalizability could

[80] This is not to call into question the decision of the REB about the AD-DBS trial. They may have agreed that the translational distance was not sufficiently minimal, but decided that the potential value of the research as designed was sufficient to provide a favourable ratio of risks to possible benefits. There are many factors that influence the decisions of REBs and I touch on only a few of them here.

not itself have justified asking AD-diagnosed participants to undergo such risks. Thus, it cannot be argued that the risks were minimized for this participant group because the technology was implanted for clinical purposes. Therefore, the potential evidence generated by the obesity-DBS protocol *as amended* about the obese participant *cannot* be used to justify conducting research in AD-diagnosed participants, until further evidence about the generalizability of those results is obtained. Until there is evidence that what worked in this case is also likely to work in their case, the translational distance between the obese participant and the AD-diagnosed participants remains too great to justify using the results from the one to justify (risky) research with the latter.

To summarize, while the obesity-DBS protocol *as amended* may have inspired the new research direction, it did not provide potential [veridical] evidence for the hypothesis being tested in the AD-DBS Phase I trial. More specifically, the potential evidence about the obese participant generated by the obesity-DBS protocol *as amended* is not, even after the AD-DBS Phase I trial's completion, veridical evidence for the hypothesis that stimulation near the fornix can "alter activity in medial temporal memory circuits, thereby providing a safe and potentially beneficial effect on memory" in AD-diagnosed participants (Laxton et al., 2010, pp. 522–533). Rather, the results of the obesity-DBS protocol *as amended* contributed what is better described as collateral value than regulatory value to the AD-DBS research.

Consider the description of the connection between the two studies given in the report on the Phase I AD-DBS trial:

> These preliminary observations in a single subject support the notion that the neural elements subserving certain memory function are accessible in humans, and that it is feasible to modulate their activity using electrical stimulation of the fornix/hypothalamus. (Laxton et al., 2010, p. 522)

The "preliminary observations" are the substance of the potential evidence produced by the obesity-DBS protocol *as amended* and the "single subject" is the obese participant. The potential evidence did not support a hypothesis about the probable effects of DBS in AD-diagnosed participants in the Phase I trial, but rather supported a "notion" that led them to believe the hypothesis was "feasible." The potential evidence was evidence, rather, for hypotheses about the accessibility of memory functions by way of DBS in humans and about the effects of stimulating neural regions that are part of the memory circuit. These hypotheses are of collateral value to the AD-DBS research program.

For instance, Lozano and his team have further hypothesised that stimulation can restore or inhibit the neurodegeneration that leads to the loss of memory function in AD patients. To justify this hypothesis, they have drawn upon the potential evidence generated by the obesity-DBS protocol *as amended* as well as additional theory. The obesity-DBS protocol *as amended* included post-operative functional imaging of the participant's brain that suggested the stimulation was driving activity through neural regions associated with the memory circuit (Hamani et al., 2008a, p. 123). In respect to theory, Lozano and colleagues have argued for a model of AD that associates the memory deficits experienced by AD-diagnosed patients with what is known as the "default mode network" (Lykestsos et al., 2012). The default mode network includes several regions of the brain connected in a circuit of activity present during

the resting state that disappears when the brain becomes actively focussed on a task (Buckner, 2012).[81] Correlations between the regions of the brain most affected early on in patients diagnosed with AD and those regions associated with the default mode network have led some to suggest that the symptoms of AD result from the impact of neurodegeneration in places that disrupt it (Buckner, Andrews-Hanna, & Schacter, 2008, pp. 28–30; Koch et al., 2012, p. 467). If this is the case, then AD is better seen (and treated) as a system-based disease:

> This approach considers AD from the standpoint of being a circuit disorder in which localized dysfunction arising secondarily to AD pathology has long-reaching consequences transmitted across an extensive brain network[, the default mode network]. (Lozano and Lipsman, 2013, p. 415)

In turn, DBS is already known to modulate neural activity, and the recent research by Lozano's team has further demonstrated that, "fornix DBS drives activity transynaptically across the circuit of Papez and the default mode network" (Laxton et al., 2010; Lozano & Lipsman, 2013, p. 415). If AD symptoms arise from disruptions within the default mode network, and DBS can drive activity through that network, increasing local function as well as preventing or slowing the degeneration of neurons kept active, then DBS is an appropriate way to treat AD symptoms. Thus the potential evidence produced by the obesity-DBS protocol *as amended* has collateral value, having contributed to and possibly changed theory about AD and DBS.

However, the argument above depends on multiple assumptions that have yet to be proven, about the nature of AD and the potential functional effects of the biological changes

[81] For this reason, as Buckner tells the story, the discovery of the default mode network was delayed: the network presented rather as a difficulty for those wishing to establish a baseline of neural activity from which they could assess increases in activity during active tasks. As such, it was ignored as a system in itself until several articles were published at the turn of the last century, highlighting its role in cognitive function.

being observed in preclinical and early phase research. For example, preclinical research has suggested a relationship between stimulation and the process of neurogenesis in the hippocampus (Encinas et al., 2011). This has prompted researchers to suggest that, "Although DBS of the fornix…is a very novel strategy, it is potentially an important therapeutic approach to slowing AD as it may slow fornix degeneration, influence hippocampal neurogenesis, and sustain cortical neurons and circuitry by releasing trophic factors" (Lykestsos et al., 2012). In other words, they claim that the preclinical evidence demonstrates that driving neural activity (increasing glucose utilization by neurons) with stimulation may not only slow neurodegeneration but can, possibly, initiate the rebuilding of neurons (neurogenesis) in an area already affected by neurodegeneration.

In addition, in the conclusion of the report on the Phase I AD-DBS trial the authors provide the following caveat: "Whether DBS regulates neurotrophin expression and neurogenesis in humans and whether this occurs in the diseased hippocampus of patients with AD is not known. The availability of animal models of AD will facilitate the examination of these questions" (Laxton et al., 2010, p. 532). While there is evidence for the potential of electricity to stimulate neurogenesis from preclinical experiments conducted with mice (Lozano & Lipsman, 2013, p. 415), the mice in the experiment cited were stimulated at a different neural target than the fornix. This preclinical research with mice suggested "a causal relationship between stimulation-induced promotion of adult neurogenesis and enhanced spatial memory"—not a causal connection between stimulation of the fornix and improved recall memory (Stone et al., 2011). The preclinical research is thus inconclusive in relation to the hypothesis. A further consideration is that because animal models for neurodegeneration are created by administering toxins, they may differ in important but undetermined ways from humans who experience disease-based neurodegeneration over time (Hescham et al., 2013, p. 2673).

Finally, recall that the evidence so far garnered from AD-DBS research does not confirm the fornix as the optimal target for stimulation in AD participants. Researchers at diverse sites have been and continue testing different neural targets, such as the frontal lobe, because they think the effects of stimulation at that region are more likely to produce the desired therapeutic effects (Neergaard, 2013).[82] In conclusion, despite considerable optimism and increasing numbers of researchers getting involved, "it is still premature to conclude that DBS can be used in the treatment of AD, and the field will wait for the results of ongoing clinical trials" (Hescham et al., 2013, p. 2673).[83] Thus, while the potential evidence produced by the obesity-DBS protocol *as amended* may contribute collateral value, there is still considerable work to be done to minimize the translational distance between that potential evidence and the inferences being made about AD and DBS. It is not yet and may not be potential evidence for any particular or valuable hypothesis.

In conclusion, the translational distance between the obese participant and the AD-diagnosed participants remains too great to justify testing the generalizability of the results of the research with that obese participant to the new, AD-diagnosed, patient group. Using that potential evidence to justify research to test that generalizability in that group presents a circular argument. The AD-diagnosed participants cannot be asked to undertake the risks of implanting DBS technology to demonstrate that generalizability. Research that requires them to undertake those risks must presume that generalizability to be justifiable. What needs to be done, and what the AD-DBS researchers are doing in their efforts to acquire further

[82] See (Hescham et al., 2013) for a recent and thorough review of preclinical and clinical research testing stimulation at different targets with the goal of developing a DBS intervention for AD.

[83] Against the potential counterargument that, because the AD research has reached Phase II we can now safely assume it will continue forward toward a therapeutic outcome I first raise the well-known fact that Phase II is no guarantee of Phase III, and also the recent halting of a Phase III trial for DBS as an intervention for Major Depressive Disorder, for reasons of futility.

empirical and theoretical justification for their hypotheses, is to minimize the translational distance between that potential evidence and the hypotheses they want to use it as potential evidence for. The potential evidence produced by the obesity-DBS protocol *as amended* in regard to memory and DBS does not, I argue, have regulatory value in respect to the AD-DBS research program. The potential evidence may yet contribute collateral value, but the translational distance between the results of the obesity-DBS protocol *as amended* and the hypotheses recently generated about AD and DBS remains too great to tell what the content of that value will be.

5.4.a.iv As a Contribution to Neuroscience

Should the translational distance be narrowed between the obesity-DBS results and the AD-DBS research, it would be by efforts made to show that the potential evidence produced by the former is evidence, for example, for the developing theory about AD and DBS that grounds the justification for the latter. That is, the potential evidence produced by the obesity-DBS protocol *as amended* may be evidence for a number of hypotheses about whether DBS can drive neural activity, and whether the causal relationship that led to (some) enhancement of the obese participant's memory is generalizable beyond that single case. This kind of collateral value is desirable, in particular within a field of research such as experimental DBS, where greater predictability is needed to reduce the risks to human participants.

The results of the obesity-DBS protocol *as amended* could be potential evidence for a generalizable, causal connection between the stimulation of the brain near the fornix, the enhancement of the participant's ability to remember a past event, and the capacity of stimulation to drive neural activity. This potential evidence could result in veridical evidence, once it is proven that the causal connection inferred can indeed be generalized to other human

brains. As such, it may be a strategic datum, upon which theorists and empirical researchers can build. It may add to or otherwise change prevailing theory about, for example, the mechanism of DBS, or the functions of the human brain.

It is possible to see the case of the triggered memory as having contributed knowledge to theory about the mechanism of and (consequently) potential therapeutic uses for DBS. As well, it may be potential evidence for future hypotheses about the functions of the brain, the memory circuit and the relationship between neural function, neurogenesis and electrical stimulation. Recall that in the Phase I AD-DBS trial two participants who were stimulated at their fornix experienced similar déjà vu type phenomena, describing memories of real past experiences.[84] They thereby repeated the original observation and thereby provided further potential evidence that the observed causal link is generalizable to at least some other humans. There remain questions to be asked about the meaning of that causal link for neuroscience and neuropathology, some of which have been addressed above.

But, for the results of the obesity-DBS protocol as amended to have collateral value in this broad sense—for then to act as potential evidence for hypotheses valuable to neuroscience, neuropathology and to our understanding of how DBS works—more research is required. The generalizability of the results of the obesity-DBS protocol as amended must be established. Testing of the hypotheses must be done in suitable participants—for example, in participants with healthy brains in respect to memory, or in AD- diagnosed participants, depending on the hypothesis at hand—for the translational distance to be sufficiently minimized. But not all of the

[84] The researchers had the participants and their spouses later confirm that the memories reported depicted real past experiences (Laxton et al., 2010, p. 524).

research that will narrow the translational distance must be DBS research involving humans; preclinical research and basic neuroscientific research already inform hypotheses in DBS research and will continue to do so.

Finally, the results of research ought to be disseminated, to maximize the opportunities for the broader epistemic community to take up the potential evidence into their own research programs, on memory, DBS, and the neuropathology of human disease. This step has been accomplished by the publication of the 2008 case report and subsequent use of the case of the triggered memory in the literature. But if the results of the obesity-DBS protocol *as amended* are to be appraised as having contributed to a process of serendipitous discovery, as it is hoped, their usefulness as potential evidence for multiple hypotheses—and thereby their collateral value—must be demonstrated.

5.4.b Conclusions

In conclusion, the most appropriate use for the potential evidence produced by the obesity-DBS protocol *as amended* is to further research into the relationship between DBS, its capacity for driving neural activity, and its effects on memory functions. That is, the most valuable contribution that this potential evidence can make would be as a contribution of useful data for a new research program about memory and DBS. It is possible that this unexpected observation of a triggered memory may be taken up into a process of serendipitous discovery in neuroscience, broadly speaking, psychology, psychiatry, or another field. My focus here, however, is on the possibility of a serendipitous discovery in medicine: the potential for a valuable discovery of a therapeutic option for AD patients is the most significant projected value of the case of the triggered memory in the literature, and so I narrow my focus to the potential value of the case in respect to clinical research. As a result, I conclude by engaging the values of the relevant epistemic community, in which a serendipitous discovery may occur: the

community of clinical researchers.

5.5 Assessing Value in the Context of Clinical Research

A research program of potential value to the epistemic community of clinical researchers would be, for example, a program that aimed to minimize the translational distance between the evidence produced from the obesity-DBS protocol *as amended*, and the relevance of that evidence for the selection of future research participants for DBS research. Depending on the ultimate outcome of such a research program, the unexpected observation of the triggered memory may or may not be part of a process leading to a serendipitous discovery in medicine.

As indicated above, for the potential evidence produced by the obesity-DBS protocol *as amended* to be taken up by the epistemic community of clinical researchers it must contribute something of value to the processes of clinical research and medicine. In the previous section, I looked to the potential value of this potential evidence in relation to the contribution it could make to the ongoing processes of research. A further consideration in the context of clinical research, however, is whether those processes of research will ultimately result in actual gains in medicine—that is, whether the results can be applied in medicine to improve the practice of medicine and the health outcomes for patients.

Sometimes, as in the case of the triggered memory, human participants are required for the research that produces potential evidence in response to an unexpected observation. That research, because it involves humans, must meet the standards of value—epistemic value as well as ethical value—of clinical research. Evidence-based medicine is the overarching framework that has led to the dominance of study design in assessments of the value of clinical research. Valuable clinical research produces valuable evidence that leads as directly as possible to knowledge that can be used by medical practitioners in determining best

practices for the diagnosis and treatment of their patients. As Kimmelman points out, this is often conceived in terms of regulatory value, a standard of value that translational or early phase clinical trials often fail to meet. But minimal translational distance between the evidence for the design of the study and the projected value of the evidence the study will produce can only be established by careful consideration of both the evidence at hand and the trial's proposed design. It is unlikely that such assessment can be made reliably or accurately in the moment, let alone intraoperatively whilst brain surgery is being performed.

5.5.b The Paradox of Control and Implications for Clinical Research

Part of the reason for the primacy of design in ethical clinical research is that time and thoughtfulness is required in the assessment of proposed protocols for research with human participants. This control is meant to prevent any particular individual or any particular decision from causing harm to a human participant, by giving the processes of assessment over to formalized groups and by requiring scientific justification for a protocol that researchers and participants then commit to following.

Therefore, the paradox of control typical of serendipity (§ 4.3) presents a potential obstacle in the way of serendipitous discovery when the relevant unexpected observation occurs during clinical research, in a human participant. Whilst it seems possible to control, in some way, for the production of potential evidence, it is not actually possible to control for serendipity. Because serendipity cannot be controlled for, it is difficult to say how it would be possible to ensure an opportunity to follow up on potential serendipity is being taken advantage of ethically. The value of the potential evidence cannot be assessed in terms of projected outcomes, and cannot be determined reliably without thoughtful and independent review.

The amendments made to the obesity-DBS protocol to produce potential evidence from the observation of the triggered memory are an example of research contributing collateral

value. However, because the capacity for accommodating that unexpected observation and its follow- up was not built into the design of the obesity-DBS protocol, the amendments were made *ad hoc*. The researchers therefore took advantage of opportunities in their efforts to maximize the epistemic value of their research, but this may have put them in conflict with other tenets of clinical research ethics, for example the need to obtain fully informed consent from participants. REBs are to approve the design of proposed clinical trials; consent is to be formally obtained before the trial begins. Making ad hoc changes to a trial's design therefore stands in conflict with the regulatory frameworks used to assess the ethical acceptability of a proposed trial. In the next chapter, I explore the implications of this for the ethics of serendipity, specifically in the context of early phase or first-in-human clinical research.

Chapter 6: The Ethics of Serendipity in Clinical Research

6.1 Basic Science and Clinical Research

Researchers need to be able to recognize the potential value of an unexpected and yet significant observation and to take action to produce potential evidence (based on this unexpected observation) in order to make a serendipitous discovery. When researchers take advantage of an unexpected observation as an opportunity to produce potential evidence, they can be recognized by their community as having sagacity. Some communities more than others will encourage their members to perceive the potential value of unexpected observations, support the agency of their members, and ensure access to the results of research. The case of the triggered memory, a case of early phase clinical research with DBS technology, takes place in a community that enables such discoveries.

However, the requirements for ethical clinical research may restrict the ability of researchers to take advantage of unexpected observations. More than potential epistemic value is needed to justify research with human participants, and even highly valuable opportunities may have to be forgone if the research cannot be performed in an ethical manner. In this chapter, I explore these and other ethical issues through the case of the triggered memory.

Put simply, mould and humans differ in important ways. It is commendable that Fleming took the mould he happened upon, tested it and manipulated it to confirm his insight into its significant properties, and then distributed data about it and cultures of it to other labs. But it would not be ethically acceptable to manipulate, experiment upon and distribute data about a person in the same way, no matter how interesting she was, unless these actions were part of a

properly designed and REB approved clinical trial for which her consent had been obtained. The Kantian principle of respect for persons is a generally accepted ethical principle in medicine. The principle demands that individual humans be treated as autonomous 'ends in themselves' and never merely as means. As humans, we have our own goals, values and desires that guide our actions, making us different from mould in a morally important way. Unlike when we use mould as a test subject in our experiments, when we use human beings to pursue research ends we ought to ensure that we do not ignore their own goals, values and desires in the process. To reduce another person to the value she has for us as a means to obtain our own ends is to fail to respect the value she has as an individual person, or to use her merely instrumentally. Making an unexpected and yet significant observation in a human, no matter how significant, does not in itself justify pursuing further confirmation of that observation by using that human merely instrumentally. Rather, further action must be taken within the context of a properly designed and REB-approved clinical study for which each participant's consent has been obtained.

The basic requirements for ethical clinical research have been framed as seven criteria, by Ezekiel Emanuel, David Wendler and Christine Grady (2000) in their now classic article "What Makes Clinical Research Ethical?" These criteria are as follows: Clinical research with human participants must contribute *value*, either in terms of improved health or knowledge gained. It must be scientifically *valid*, in terms of methodological rigour, and participants[85] should be *selected fairly*, for scientific, objective reasons. There must be a *favorable 'risk-benefit ratio'*—the benefits to individuals or to society generally must outweigh the risks borne by participants; effort must be made to minimize risk and maximize benefits. Trial design must be assessed for

[85] The article by Emanuel, Wendler and Grady uses the term "subject" where I use participant: within that article the authors themselves provide a good argument for using participant instead of subject, with which I agree (Emanuel et al., 2000, p. 2707).

these criteria by *independent review*. Selected participants must voluntarily participate, a criterion demonstrated by the obtaining of their *informed consent*. And finally, participants must be *respected*—their privacy, the continuing voluntariness of their participation and also their well- being should be of concern to researchers during both the design and implementation of clinical studies (Emanuel et al., 2000).

Pursuing a chance, unexpected observation in a clinical trial in order to produce potential evidence may interfere with a study's ability to meet the criteria outlined above for ethical clinical research in cases of potential serendipity within the field of contemporary DBS. In this chapter, I demonstrate this by showing first that the original obesity-DBS protocol, during which the memory was triggered, is a particular kind of clinical research: early phase research with a therapeutic aim. The therapeutic aim of the early phase research in this case was primary to the secondary epistemic aims, and so the therapeutic aims directed both the design and decision-making. Because it has both therapeutic and epistemic aims, the original obesity-DBS protocol is comparable to interventions that fall under the category of non-validated practice (interventions) theorized by Robert Levine. I follow Levine in arguing that non-validated interventions should be subject to the regulations of clinical research. This does not entail eliminating or reducing the influence of the therapeutic aims.

Second, I demonstrate that the obesity-DBS protocol *as amended* reflects the addition of a new, purely epistemic aim to the original study.[86] Because the amendment to the original protocol was made with a purely epistemic aim, unrelated to the health needs or particularities of the obesity-DBS protocol participant, the resulting obesity-DBS protocol *as amended* represents a distinct direction of research from the obesity-DBS protocol as originally designed

[86] For a detailed description of the protocol, refer to § 5.2.b.iii.

and approved. I then unpack the implications of this distinction. This shift in the goals of the research affects how potential serendipity should have been ethically accommodated when it arose.

Third, I look to the criteria for ethical clinical research, building on the distinction between the aims of the obesity-DBS protocol and those of the obesity-DBS protocol *as amended*, and raise concerns about possible conflicts between ethics and serendipity. I argue that the addition of new epistemic aims and changes to the original protocol required prospective research ethics review by an REB. Arguments must be given to demonstrate that any new clinical research involving humans is ethical, including research with humans that results from an unexpected observation being made in a human. I refer to six of the seven[87] criteria for ethical clinical research identified by Emanuel and colleagues – value, scientific validity, fair participant selection, favourable harm-benefit ratio, REB review and informed consent—to demonstrate that justifying the use of the obesity-DBS protocol participant in the obesity-DBS protocol *as amended* is not straightforward. Finally, I suggest methods for encouraging serendipity without compromising ethics in early phase research.

6.2 The Case of the Triggered Memory as Clinical Research

6.2.a The Obesity-DBS Protocol as Clinical Research with Therapeutic Aims

Clinical research with human participants differs in morally significant ways from therapy, or medical practice (e.g.: Miller & Brody, 2003). Ideally, in medical practice: patients are expected to benefit from the therapeutic interventions they undergo; therapies are prescribed to just those patients who need them; and physicians have confidence about what outcomes to

[87] I do not discuss the issues of privacy and confidentiality in this chapter, as they do not present challenges unique to this case.

expect from therapeutic interventions. Therapies are prescribed primarily if not always solely to benefit the patients to whom they are prescribed. In clinical research, by contrast, participants are not necessarily expected to benefit from the interventions they undergo. Indeed, the research is being undertaken because there is disagreement about the potential benefits of the intervention. Most importantly, research is done in order to generate generalizable knowledge—primarily to benefit medicine, or society, and not necessarily with the intent to benefit particular participants enrolled in clinical trials (Baylis, 1993; Miller & Brody, 2003). Participants are selected for interventions in research because they meet selection criteria determined on the basis of the value and validity of the study.

However, the divide between therapy and research in medicine may not be sharp (e.g.: Wendler & Miller, 2007). Clinical research can be conducted in such a way as to also benefit its participants, and medical practice can have epistemic outcomes (Kimmelman, 2007). Kimmelman argues that the design of clinical research protocols can and should be guided by therapeutic goals. Even when secondary to the epistemic goals of research, therapeutic goals can legitimately influence decisions about design and implementation of clinical research. Kimmelman suggests the following analogy:

> If my primary goal in a shopping run is to pick up bread, and my secondary goal to buy cheese, the secondary goal may constrain my choice of bakery, and consequently my choice of bread. Similarly, secondary therapeutic goals can and should influence the investigator's choice of research design. (Kimmelman, 2007, pp. 38–39)

As Kimmelman argues, in clinical research it is legitimate for the design of a protocol to be guided by both therapeutic and epistemic goals. The legitimate influence of therapeutic goals on the design of a research protocol can be seen in the design of the original obesity-DBS

protocol. For instance, the 2008 case report summarizes the primary intention of the obesity-DBS protocol as therapeutic: “Bilateral hypothalamic deep brain stimulation was performed *to treat a patient* with morbid obesity” (Hamani et al., 2008a, p. 119, emphasis mine). The primary goal of the intervention was therapeutic—to modulate the appetite of the participant and resolve his problematic eating behaviours. The secondary goal of the obesity-DBS protocol was epistemic—to produce generalizable knowledge about the safety and functional effects of stimulating the hypothalamus. The therapeutic goal directed the choice of neural target in the protocol’s design, and in practice directed the titration of the DBS to reduce interfering or negative side effects and to maximise any possible benefits. As Kimmelman points out, a study can have therapeutic as well as epistemic goals and still be classified as clinical research and should be regulated accordingly.

The obesity-DBS study and studies like it are a particular class of early phase clinical research as a result of this intersection of therapeutic and epistemic aims. One key difference between this kind of research and other kinds of clinical research can be highlighted by looking at how criteria for participant selection are determined. Typically in registered and multi-phase clinical trials, for example, a protocol is designed and approved by a REB, and then researchers enroll participants that meet predetermined selection criteria. The participant selection criteria for clinical studies are devised for scientific reasons, to ensure the value of the study to the relevant patient group by selecting participants from that group, or to ensure the validity of the results by controlling for comorbidities. For the obesity-DBS protocol, however, the participant was not selected according to pre-established requirements of the study, but rather the study was designed for this participant.

Further, the participant was referred to the neurosurgical team for treatment options: “Given his resistance to treatment, the concern with the long-term health consequences of

morbid obesity, and our group's long-standing interest in functional neurosurgery and DBS, he was referred to consider the possibility of a neurosurgical treatment" (Hamani et al., 2008a, p. 119). The basis for the REB's approval was both the treatment-resistant status of the participant, "and the possibility of reducing the health risks of chronic obesity should the intervention prove successful" (Hamani et al., 2008a, p. 119). Part of the measure of success of this protocol was the potential positive effect on the participant's obesity (Hamani et al., 2008b, p. 1). The design and goals of the obesity-DBS protocol thus emerge from the context of medical practice and therapy, even if the protocol itself was conducted within the context and under the regulations of clinical research.

A suitable category for comparison is the category of "nonvalidated practices" described by Robert Levine (1988), or what I will call non-validated interventions.[88] Levine's category denotes a medical practice with therapeutic intent for which there is insufficient evidence as to its safety or efficacy. These can be novel practices, or practices that were once generally assumed to be safe and effective but about which there is now doubt. The community of experts, medical practitioners, do not yet or no longer agree about the safety or efficacy of that practice, and so cannot be confident about what will happen if they prescribe the intervention for individual patients (Baylis, 1993, p. 52-53; Caniano & Baylis, 1999, p. 307). Levine uses this category to highlight the need for validation, by conducting research, before (re-)according these practices the status of therapy (Levine, 1988, pp. 4–6).

[88] I choose "interventions" as the more neutral term, to avoid confusion between the case I am working with, which is a case in clinical research, and the context of medical practice. Thus my choice does change the meaning of the term slightly from Levine's intention: he was referring to practices, within the context of medical practice, while I use the term "intervention" to indicate that it could be in the context of practice or, as in the case studied here, the context of research. Intervention is meant to include therapeutic intent in its meaning, but to avoid entailing practice.

The obesity-DBS protocol can be described as a non-validated intervention. *Unlike* Levine's category, the implementation of the obesity-DBS protocol took place in a context of research rather than practice. The protocol was designed and regulated as a research study, and researchers were explicit about their uncertainty about the safety and efficacy of this intervention for this participant. *Like* non-validated interventions that arise in the context of medical practice, the obesity-DBS protocol was thus similar to therapy in intent, but was not therapy (Baylis, 1993, p. 52-53). For the obesity-DBS protocol, therapeutic intent—an intention to directly benefit the participant himself, if possible—influenced both the design and the implementation. This particular participant's needs guided the design of the protocol he participated in. The benefit of using the category of non-validated intervention to describe the DBS-obesity protocol is that it highlights the fact that there were both therapeutic and epistemic aims guiding the design and implementation of that protocol. Further, in comparison with clinical research for which suitable participants are selected after the trial has been designed and approved, in this case therapeutic aims determined the design of the study and acted as its primary goal.

2.c. The Obesity-DBS Protocol *as Amended* Includes Additional, Epistemic Aims

While the particular needs of the participant in the original obesity-DBS protocol informed the design and the implementation of the protocol, they did not inform the obesity-DBS protocol *as amended*. Rather, the reasons why this particular participant was the subject of the amended protocol were the facts that he was already participating in the obesity-DBS research and that he was the source of the unexpected observation. The obese participant did not suffer from a memory-related disability, and the study of his memory was clearly distinct from the original goal of the obesity-DBS protocol, namely to control appetite. The aims of the

memory-related amendments to the obesity-DBS protocol, as described in the 2008 case report, were only for the generation of generalizable evidence:

> This study shows that electrical stimulation of the hypothalamus modulates limbic activity and improves hippocampus-dependent memory function … just as DBS can influence motor and limbic circuits, it may be possible to apply electrical stimulation to modulate memory function and, in so doing, gain a better understanding of the neural substrates of memory. (Hamani et al., 2008a, p. 123)

Clearly, the amendments to the original-DBS protocol (to follow up on the observation of the triggered memory) changed significant features of the obesity-DBS protocol approved by the REB and consented to by the participant and for this reason required independent ethics review. A brief consideration of the criteria for ethical clinical research as described by Emanuel and colleagues will show that the amendments to the original REB approved protocol likely warranted separate REB review of a new protocol and following this a new consent to participation in the obesity-DBS *as amended* protocol.[89] With the original obesity-DBS protocol there is reason to believe that the participant's consent was motivated by a desire to control his appetite. There is no reason, however, to believe that this desire would have motivated participation in the obesity-DBS *as amended* protocol.

A hunch or insight into potential value cannot alone justify conducting clinical research involving humans—measures must be taken to ensure that the research itself is also ethical. Similarly, the insight that the triggering of the participant's memory may indicate the existence of an important causal relationship does not in itself justify conducting that research in that or

[89] As I will show, a separate study with purely epistemic aims could have been proposed, reviewed by the REB and then implemented in addition to—or, to use Paul Ford's term, "piggybacking" on—the obesity-DBS protocol (Ford, 2006).

any participant. Rather, the research required to confirm an insight—to produce potential evidence—also needs to meet the criteria for ethical clinical research involving humans.

6.3 Meeting the Criteria for Ethical Clinical Research

In the following sections, I look to the criteria for ethical clinical research laid out by Emanuel and colleagues (2000) to address questions about whether the obesity-DBS protocol *as amended* meets the standards for ethical clinical research they present.

6.3.a Social or Scientific Value

Emanuel and colleagues list value as the first and primary criterion for ethical clinical research. Joseph Fins argues that there is an imperative to maximise the knowledge gained whenever implanting DBS technology, not only because of ethical concerns but also because of the potential value of DBS in terms of the epistemic contributions it can make to neurological knowledge (Fins, 2012). As a device that modulates the neural function of humans, DBS offers a unique opportunity to produce evidence about brain functions, the etiology of neurological disorders, and the impact of stimulation on both of those: "They are a means of inquiry that allow us to "probe" the inner circuitry of the brain while we pursue therapeutic goals" (Fins, 2012, p. 4). The social and scientific value of the obesity-DBS protocol, if we agree with Fins, would be enhanced by the amendments made in the obesity-DBS protocol *as amended* because those amendments contribute additional epistemic aims relevant to improving our understanding of the brain. That is, the obesity-DBS protocol *as amended* adds collateral epistemic value to the therapeutic and epistemic aims of the obesity-DBS research.

However, if this collateral value is assessed according to the projected outcome of its usefulness in AD research, then the translational distance between that evidence and the

justification for selecting the AD-diagnosed participants in that research is the means by which it ought to have been assessed. As I argued in Chapter 5, there are reasons to believe that the translational distance between the potential evidence produced by the obesity-DBS protocol *as amended* and its projected use was too great: that potential evidence could not be seen as potentially veridical evidence for the AD-DBS therapeutic hypothesis tested in the Phase I trial. Consequently, the value of that potential evidence does not lie in its direct contribution to the processes of AD-DBS research, but rather in the potential collateral value of its use for loosely related areas of research in neuroscience and neuropathology.

But the production and the use of the potential evidence occur in two separate studies: one, as it played out in this case, the obesity-DBS protocol *as amended*; the other, the AD-DBS Phase I trial. The REB approval for the AD-DBS trial does not *post hoc* assign value to the obesity-DBS protocol *as amended.* So the value that the potential evidence eventually has as justification for further research with other participants, and the value of *producing* the potential evidence so that it can be put to such use, ought to be assessed separately. I show in the following sections why justification for doing the research with the obesity-DBS participant to produce that potential evidence ought to have been approved and assessed in its own right, before that potential evidence could have been ethically produced.

6.3.b Scientific Validity

Clinical research must be scientifically valid so that research participants are not asked to put themselves at risk as part of an exercise likely to generate invalid results (Emanuel et al., 2000, p. 2704). Clinical research ought to be designed according to accepted scientific principles, and use accepted methods and "reliable practices," so that projected outcomes can be predicted with some probability. Further, validity requires a proper sample size. Too few participants means the results will not be significant or reliable. Too many participants means

that more people are exposed to the risks of research than necessary to generate new knowledge. In sum, the design of research must be scientifically valid, so that clinical research produces results that actually answer valuable research questions.

Whether the methods and power of a proposed study are acceptable is something to be assessed during an independent research ethics review. But scientific validity also affects the criteria for fair participant selection. For instance, for a clinical study to be valuable and scientifically valid, the participants (1) must have the characteristics needed for the hypothesis to be tested by the research, and (2) must produce results that are generalizable to others in their patient group or beyond. In respect to (1), the obesity-DBS participant was ideal for the obesity-DBS protocol *as amended*. In respect to (2), questions can be raised.

The suitability of the results of research as evidence for other hypotheses, assessed in relation to estimates of translational distance, is one way to judge whether there are scientifically valid reasons for selecting particular participants or groups for a clinical study. For example, if the value of producing the potential evidence was limited to its use as evidence for a hypothesis regarding its application in the cohort of AD-diagnosed participants in the AD-DBS trial, I have argued that participants who share more characteristics with that group of AD-diagnosed participants may have minimized the translational distance between evidence and hypothesis sufficiently for regulatory value. As well, I advised a better approach would have been to consider the value of the potential evidence produced by the obesity-DBS protocol *as amended* in terms of potential collateral value. To affirm its collateral value, the potential evidence must still be shown to be generalizable, however. Thus, the relevant potential evidence—that hypothalamic stimulation can drive neural activity in the memory circuit—did not have to be produced via research involving the participant from the obesity-DBS protocol to be scientifically valid in respect to its potentially valuable outcomes.

While the obesity-DBS protocol *as amended* may have employed scientifically valid methods for producing results about the memory enhancement experienced by the obese participant, it produced results relevant to that single case only. A valid use of that potential evidence for further research involving humans requires that it first be generalized so it is sufficiently robust. Generalizability can be ascertained either by testing its replicability in humans who have healthy brains (in respect to memory), or, for example, in participants experiencing memory loss and for whom they are hoping to benefit with an intervention based on that potential evidence.

6.3.c Fair Participant Selection

Fair participant selection is important in ethical clinical research because it calls attention to the potential for influences beyond scientific validity to affect researchers' preferences for recruiting participants from some groups. The criterion of fair participant selection thus demands that, "scientific goals for the study, not vulnerability, privilege or other factors unrelated to the purposes of the research, be the primary basis for determining the groups and individuals that will be recruited and enrolled" (Emanuel et al., 2000, p. 2705). Fair participant selection, however, also requires that individuals and groups not be excluded from participating in clinical research for other than scientific reasons, or because they are particularly susceptible to the risks involved (Emanuel et al., 2000, p. 2704).

In respect to the criteria for scientific validity and fair participant selection, the obese participant was a suitable candidate for the obesity-DBS protocol *as amended*, but he was not the only possible candidate for that research. Any participant who had DBS technology implanted at the relevant site near the fornix would have been a valid participant in research conducted to demonstrate the replicability of the memory enhancement that the obese participant experienced with stimulation. There are also no scientific reasons for excluding the

participant from the original obesity-DBS protocol from participating in the obesity-DBS protocol *as amended*. It would be fair, then, to invite the obese participant to participate in a study that was designed in response to the intraoperative observation of his triggered memory.

Since the published 2008 case report makes no mention of REB review of the obesity-DBS protocol *as amended*, it is unknown whether the participant in the obesity-DBS protocol was fairly invited to participate in the obesity-DBS protocol *as amended*. There is reason to suspect, however, that convenience played a role in the choice of this research participant for the amended research.

Convenience can be an unethical (unfair) factor for participant selection if participants are convenient as a result of a disadvantage or vulnerability, as may be true for hospitalized patients or prison inmates. Scientific validity does not preclude convenience, and nor are all scientifically valid criteria for patient selection also ethical. For example, in the Canadian context, it was recently revealed that aboriginal children at residential schools—boarding schools run by churches or the government they were once forced to attend—were effectively conscripted into research. This research included controlled experiments in malnutrition, to which the children never consented and of which their parents were never informed (Mosby, 2015). Besides the general lack of ethical conduct in this research, it is notable that the children, and other members of aboriginal communities who were used as participants in this research, were chosen as participants partly because *they were already starving*. Convenience is not only a factor of location and authority, as it is when the ethics of conducting research with prisoners is discussed. It also relates to the fact that some research is more conveniently done in participants who both meet the criteria for selection for that research, and whose risks are minimized because they are already in a less than optimal state of health or liberty.

Fair participant selection is a challenge for research involving neurosurgery and the implantation of DBS technology because this research carries with it high risks to participants (Copeland, 2013; Ford, 2009; Lipsman, Bernstein, & Lozano, 2010; Schermer, 2011). Further, the history of neurosurgical interventions (including the infamous lobotomy) is such that proposals for an intervention that includes psychosurgery (neurosurgery for the purposes of manipulating psychological functions) is likely to attract scrutiny as regards the criteria for participant selection (Bell, Mathieu, & Racine, 2009; Lipsman et al., 2010; Lipsman, Giacobbe, Bernstein, & Lozano, 2012). In general terms, Emanuel and colleagues suggest caution when participants are selected (in part) because they are convenient. This caution is particularly warranted with DBS research.

Individuals who already have the DBS technology implanted are in one sense convenient participants for research involving DBS. Even more convenient, as regards any specific DBS research protocol, are individuals who already have the DBS technology implanted in the desired neural location. As regards the obesity-DBS protocol *as amended*, the participant in the original obesity-DBS protocol was the ideal participant – he already had the DBS technology implanted and he already had this implanted in the desired location. To say the least, he was a convenient participant for the amended research.

To compare, convenience partly led Fleming to continue testing the mould he found rather than try to find another sample to work with, and it partly led Marshall to follow up with the patients whose lab results he had initially observed before he enrolled new participants in a new trial. But there are also good reasons for Fleming and Marshall to have preferred *that mould* and *those patients* that go beyond convenience. Having made the original observation of *that mould* and *those patients*, Fleming and Marshall respectively could have confidence that their further examination would bear relevant results. Similarly, the Toronto team had reason to

believe the methods for confirming the causal connection inferred when the memory was originally triggered in the obese participant are more likely to be effective in *that participant*, where the neural target is guaranteed to remain consistent.

However, confirming there was a causal relationship between memory enhancement and stimulation near the fornix within the obesity-DBS participant is only one step toward demonstrating the replicability of those results. Generalizability to other cases is an important part of establishing the validity of that potential evidence as evidence for hypotheses about how DBS may affect other peoples' brains and memory. Fair criteria for participant selection for research intending to replicate the effects of DBS on memory observed in the case of the triggered memory would not have excluded, but would not necessarily have included, the obese participant. Fair criteria for the selection of participants for the research done to produce potential evidence in response to the triggered memory—including the obesity-DBS protocol *as amended*—should have been approved by an REB before anyone was invited to participate.

6.3.d Favorable Ratio of Risks to Possible Benefits

The three conditions for a favourable risk to possible benefit ratio laid out by Emanuel and colleagues are the following: "the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks" (Emanuel et al., 2000, p. 2705). Where the risks and likely benefits are especially uncertain, as in early phase and first-in-human research, then reviewers of the proposed research must perform a calculation of the *estimated* risks and *estimated* possible benefits and assess if the estimated possible benefits to individual participants and to society as a whole can justify the estimated risks to the individual participants. Such calculations lack a "settled

framework" or standardized method, but the calculations remain important. If the estimated risks of the research to participants are not judged to be worth the estimated possible benefits to the individual participants or to society, then the research is not justifiable (Emanuel et al., 2000, p. 2706).

Emanuel and colleagues suggest that risks can be minimized, for example, "by using procedures already being performed on [participants] for diagnostic or treatment purposes" (Emanuel et al., 2000, p. 2705). It can thus be argued that, because the original participant from the obesity-DBS protocol already had the DBS technology implanted, selecting him to participate in the obesity-DBS protocol *as amended* minimized the harms done and the risks taken by human participants overall. For example, if another individual who did not already have that technology implanted were to be enrolled in a study to confirm the causal relationship between memory function and stimulation of the fornix, the risks to that participant from the neurosurgical procedure alone would far outweigh the potential benefits to that participant. The risks of participation in the obesity-DBS protocol *as amended* to a participant requiring the implantation of DBS technology would be far more than the risks to the participant who already had the technology implanted.

When a new indication for DBS is proposed, it is partly on the basis of a belief that DBS has already been shown to be safe and effective. DBS interventions are considered safe (by some) because they are reversible, when compared with other neurosurgical interventions. The stimulation can be turned off so that the technology no longer affects the person who has electrodes implanted; the stimulation parameters can be adjusted post-operatively to avoid undesirable side effects; and, in extreme cases, the technology can be removed. Further, given that the participants selected for DBS typically have exhausted other treatment options, the risks of DBS are to be compared to the risks of their disease. Thus, the risk to possible benefit

ratio for these participants (as with the obese participant) can be deemed favourable when the intervention is done with (hopeful) therapeutic intent.

But this favourable ratio does not automatically extend to additions to or a change in a protocol after the REB review is completed. Such changes may affect that ratio. For this reason, even though the obesity-DBS protocol *as amended* minimizes risks overall by "piggybacking" on another DBS procedure, it needs to be independently reviewed to ensure that the amendments do not affect the original risk to possible benefit ratio.

6.3.e Independent Review

To fairly assess whether clinical research is justifiable and ethical, independent review is required (Emanuel et al., 2000, p. 2706). REBs assess proposed studies for ethics by attending to whether the study is valuable, valid, fair and favorable in respect to the ratio of risks to possible benefits, among other things. The obesity-DBS protocol *as amended* changed the parameters by which the obesity-DBS protocol was originally assessed and approved. Independent review of one study does not carry over to other studies, including studies that may be described as "piggybacking" on ongoing and otherwise approved clinical research.

More specifically, the amendments described above to study design, markers of success, participant selection criteria and ratio of risk to possible benefit warranted a return to the REB for review before the obesity-DBS protocol *as amended* could be ethically implemented. Of particular importance to the REB would have been the shift in research design informed by a shift in research objective. The amendments represent a shift from primarily therapeutic aims guiding design and implementation, to the introduction of a novel epistemic aim which directly influenced the design and implementation of the protocol. In cases of potential serendipity, advance approval must be obtained through independent REB

review of a new research protocol (in this case, the obesity-DBS protocol *as amended*), and cannot be subsumed under the approval given for the original research that generated the relevant unexpected observation. In sum, clinical research required to produce potential evidence from an unexpected observation is subject to the same ethical standards and regulations as all clinical research.

6.3.f Informed Consent and Respect for Prospective and Enrolled Participants

Informed consent and respect for participants are widely recognised as essential for ethical research involving humans. Participants in research must be competent to give consent, fully informed of the nature of the research they are consenting to participate in, and their participation must be voluntary throughout the research process.

The point of obtaining consent is twofold: "to ensure that individuals control whether or not they enroll in clinical research and participate only when that research is consistent with their values, interests, and preferences" (Emanuel et al., 2000, p. 2706). If participants enroll in a study that is "consistent with [their] values, interests, and preferences," modifying or adding to the epistemic goals of that study may undermine the validity of their consent. For instance, participants who would willingly enroll in a study that had both therapeutic and epistemic goals may not want to enroll in a study with no therapeutic potential (i.e., no potential for direct medical benefit). Valid consent to ongoing participation in a revised study (with different research goals) is contingent on the participants being informed of, and accepting of, the revised goals. This places an obligation on researchers to solicit renewed consent from those participants. Importantly, this obligation cannot be finessed by having the original research goals defined in exceedingly broad or vague terms as to capture any and all possible subsequent revisions under some generic description.

Finally, respect for participants requires that they be provided with new, relevant

information that arises during the study, thereby making it possible for them to withdraw their consent to participate in that research without penalty (Emanuel et al., 2000, p. 2707). Transparency about any additions to or changes in epistemic intent is needed to fulfill these requirements.

6.3.g Discussion

In sum, the obesity-DBS protocol *as amended* required independent research ethics review by the REB, separate from and without relying on the justifications that garnered REB approval for the obesity-DBS protocol as originally designed. The shift from a design and implementation guided by primary therapeutic aims and secondary epistemic aims, to include an additional epistemic aim unrelated to the original aims but that also guided design and implementation, represented a shift in the ratio of risk to possible benefit, in the selection criteria by which the obese participant was invited to participate in that research, and in both the purpose and the measurement of success of the protocol. As these are some of the key parameters by which REB approval is granted, a shift in these parameters required a return to the REB. This shift in intention also required that consent be renewed (at which time participants can assess whether the new goals of the study accord with their values, interests and preferences).

The need to carefully consider factors such as value, validity, participant selection and the ratio of risk to possible benefit means that new research cannot occur immediately in response to an unexpected observation that may produce potential evidence for potential serendipity. Ethical clinical research requires REB review and approval followed by participant consent. Even if REB approval is granted for continuing research toward newly introduced epistemic aims with the same participant in whom an unexpected observation was made, the need to follow the regulations and meet the standards for ethical clinical research will have

slowed a researcher's ability to follow up. While processes of serendipitous discovery are indeed thereby slowed in the context of clinical research, unexpected observations can still be taken up into process of ethical clinical research that may foster discovery by promoting collateral value. An example of a recent study with memory using DBS recipients as participants illustrates an option for ethically following up on the unexpected observation of the triggered memory.

In 2011, a memory-DBS protocol was completed with seven participants who were receiving implants for a clinical purpose. The participants were patients diagnosed with epilepsy. In the workup to the surgical intervention to treat their epilepsy, EEG (electroencephalogram) "depth electrodes" were implanted in their brains. A "piggyback" study with primarily epistemic goals was proposed to investigate the effects of stimulation on participants' memory functions before the prescribed epilepsy surgery took place. This memory-DBS study which involved stimulation in particular regions of the brain (the entorhinal cortex or the hippocampus) looked to identify improvements in memory function at particular stages in the learning process (Suthana et al., 2012, p. 503). In many ways, this memory-DBS study with participants engaged in clinical care for their epilepsy mirrors the obesity-DBS protocol *as amended.*

The participants in this memory-DBS study were having electrodes implanted for clinical reasons—these electrodes acted as guides for a later, therapeutic surgical procedure. Thus therapeutic aims dictated the neural target for those electrodes and the length of time those electrodes would be implanted. The epistemic aims of this memory-DBS study were primary in this context, as they were in the amendments made to the obesity-DBS protocol. However, study participation was secondary to the primary reason for the implantation of the electrodes. This memory-DBS study did not select participants for implantation procedures; it

selected participants who had electrodes implanted in the appropriate neural targets. Thus this memory- DBS study—like the obesity-DBS protocol *as amended*—was clinical research with an epistemic aim, of no lasting benefit to the participants, who were selected for reasons of scientific validity because they had electrodes implanted in a particular region of their brains. What made it both scientifically valid and fair to select these participants for this research is that the memory-DBS study had a favorable ratio of risks to possible benefits. The participants were not asked to take on the risks of DBS technology implantation for the sake of this research, as they had been selected for participation post-implantation.

It is clear from the report on this study that the participants were informed of the epistemic aims of the study and that an REB had granted approval to this study. Further, the report is explicit that the consent obtained from the participants related directly to those epistemic aims and the research intended to develop potential evidence in relation to those aims (Suthana et al., 2012, p. 503). It can be presumed that the additional psychological tests relating to memory were approved because they entailed minimal further risk in relation to the possible epistemic benefits of learning more about the memory circuit and whether memory can be enhanced. Importantly, and in contrast with the obesity-DBS protocol *as amended*, the results of this memory-DBS study with epileptic participants were not irrelevant to the group selected for participation: epilepsy is a neurological disease that can have an effect on memory function (Suthana et al., 2012, p. 508). Finally, because the memory-DBS protocol is associated with (but independent from) the epilepsy protocol, it can be consented to—and withdrawn from—by potential participants without affecting their care.

The memory-DBS study that took place alongside a clinical application of DBS in epilepsy patients presents a case in which an additional epistemic goal was pursued through clinical research with DBS recipients in an ethical way. The research was approved by an REB

and consented to by its participants before the study began. Scientific validity was the primary measure for selecting participants, and because these participants already had electrodes implanted the ratio of risks to possible benefits for this study was favourable. As a "piggyback" study—a study with primarily epistemic goals that selects participants who are receiving DBS implants for therapeutic or clinical reasons—this research with patients who were receiving DBS technology in preparation for therapeutic surgery provides an alternative to producing potential evidence in an ongoing, amended study.

6.5 Concluding Remarks

In conclusion, the case of the triggered memory demonstrates how serendipity may conflict with the ethics of clinical research. In particular, the introduction of novel epistemic aims to a clinical study already in progress—what occurs when researchers immediately take advantage of an unexpected observation in a human participant as an opportunity to produce potential evidence—can compromise the research ethics approval granted for that study by an REB and the consent obtained from participants. This is of particular concern in contexts where participants may be recruited on account of being convenient.

However, as I have shown, this potential conflict with ethics does not mean that serendipitous discoveries will not be made in the context of clinical research. Rather, the account I have provided in this dissertation counters those who would claim that contemporary emphasis on ethics and REB approval in clinical research preclude progress by serendipity. Just as granting individual scientists the freedom to pursue their chosen ends will not foster serendipitous discovery in science' freedom from the constraints of research ethics will not foster serendipitous discovery in clinical research. In both cases, the fostering of serendipity must take place at the level of the community. Attending to collateral value—designing studies that "piggyback" on clinical care or research with therapeutic primary aims, for example—is

one way the community of clinical researchers can encourage serendipity without compromising ethics. As Kimmelman (2010) suggests, attending to collateral value widens the scope of possible directions in which the potential evidence generated by clinical research may go (p. 101). Clinical research that attends to collateral value and takes place in a community of researchers oriented toward fostering serendipity will provide more opportunities for unexpected observations to be perceived, for epistemic agents within that community to express their sagacity, and for serendipitous discoveries to be made.

Chapter 7- Conclusion

7.1 Summary of the argument

Serendipity is a concept with three logically necessary elements: it describes an *unexpected* observation that required the *sagacity* of some epistemic agent to recognize its significance, and that observation (eventually) resulted in a *valued outcome*. However, there are many variations on this tripartite theme. Some accounts of serendipity focus primarily on the role of chance, some accounts focus almost entirely on the role of the wise epistemic agent, and very few accounts sufficiently emphasise the importance of the valued outcome. While there are a variety of definitions of serendipity and many inconsistencies between them, I defend a tripartite account of serendipity that provides a method for identifying instances of serendipitous discovery. Serendipitous discoveries are processes of discovery in which chance and sagacity enabled an unexpected observation to be made, and that unexpected observation to lead to a valued outcome. When attention is turned to the tripartite nature of serendipity, the following conclusions become clear.

First, epistemic agency is required to express sagacity in response to an unexpected observation. Perceiving the significance of an unexpected occurrence is not sufficient to bring about a serendipitous discovery, however. An epistemic community must accept, value, and take up that observation, which in turn requires trust, respect and acceptance of one's worth as an epistemic agent. Further, serendipitous discoveries in science cannot be fully described in terms of a single individual at a particular time or place. Rather, facts about the context and

community—and the norms and biases used to define communities—are as important in a description of serendipity as facts about a chance event and the psychology of individual researchers.

Second, the category of serendipity is retrospectively applied. Because the valued outcome is an essential element in serendipity, there is no serendipity until all three elements come together in a single process. This means that the serendipitous status of the unexpected observation is indeterminate until the valued outcome is known. Which events are part of a narrative of discovery, and whether that narrative is of serendipitous discovery, are determined by factors other than the conditions in which the original unexpected observation is made. Social-epistemological factors such as the values and norms of an epistemic community determine how a discovery narrative is constructed, to what purpose and including whose contributions.

Consequently, the sagacity involved in serendipity can be understood as a category of appraisal by an epistemic community. By including an agent in a narrative of serendipitous discovery, the community appraises that agent for making a particular kind of contribution to a discovery process. Further, this appraisal is given for more than recognizing the significance of an unexpected observation. It is given for preparing, preserving and/or disseminating that observation in a way that then contributed to a valued discovery.

Sagacity is a complex concept when used to describe the wisdom of an agent who is given credit for serendipity, partly because it represents both the insight and actions of the epistemic agent that led to her making a significant contribution to a process of discovery and the positive appraisal of that agent for her insight and actions by the community. From the perspective of the narrative of discovery, and the tripartite definition of serendipity, the epistemic agency required to make a serendipitous discovery can include not only the insight

and actions relevant to the unexpected observation, but also the insight and actions relevant to pursuing the completion of a discovery process. These latter aspects of epistemic agency, however, are not always present when sagacity is.

The examples of Barry Marshall and Alexander Fleming served to illustrate this last point. As well, a look at the discovery narratives and their contributions demonstrated the effectiveness of the tripartite framework for explaining how serendipitous discoveries come about. The discovery of *H. pylori* and its relationship to stomach ulcers is often told as a narrative of linear, theoretical progress, from its origin in the unexpected observations of Warren and the insight and perseverance of Marshall. On closer examination, however, Marshall did epistemic work to produce evidence that the epistemic community took up. Not so much Marshall's dogged persistence as the acceptance of his agency and consequently the uptake of his evidence by the epistemic community enabled the discovery resulting from the unexpected observations.

Similarly, in the case of Fleming and the discovery of penicillin, a linear, progressive, individualistic account of serendipity would fail to appreciate the complexities of the discovery process. While there was sagacity involved in the insight and actions following Fleming's unexpected observation, it is also clear that it was the agency of Fleming within that community, as a lab director, teacher and author that led to the later use of that evidence by Florey and Chain to complete the process of discovery. It is easier to see with the Fleming-penicillin narrative that the connection between Fleming's unexpected observation and the valued outcome resulted from contingent factors about the context in which the discovery process took place.

These two paradigmatic cases thus demonstrate that a valued outcome is a necessary element of serendipity. As well, serendipity entails sagacity, but sagacity does not necessarily lead to serendipity: while epistemic agency is required for the completion of a serendipitous discovery process, the recognition of that agency is susceptible to community values. For instance, the recognition of Marshall as passionate instead of mad came after the scientific community accepted his ideas, which they initially resisted. Further, the recent suggestions that Fleming may not have deserved the Nobel Prize for his role in the discovery of penicillin attest to the community's role in establishing who gets credited with sagacity. Finally, my analysis of the two narratives contrasts with the idea that serendipity enables science to progress through luck, leaps and bounds: rather, the contributions Marshall and Fleming made were made through careful consideration of the scientific validity and usefulness of evidence produced during the course of research.

In philosophy of science, serendipity is described as a cause of novelty that leads to progress in science, but my analysis looks at the probable causes of serendipity by focusing on the community. Because chance is involved, and serendipity is by definition unexpected, the causes of serendipity are properly described in terms of probabilities. Some communities have features that enable them to make more serendipitous discoveries than other communities. These features increase the probability that the confluence of chance, sagacity and a valued outcome—serendipity—will occur in a single process. In particular, features of a community that increase the probability of serendipity include the following: encouraging members to take advantage of unexpected opportunities; enabling members to give and receive support for their insights while engaging in epistemic cooperation; and making new and accepted knowledge readily available to all members of the community. Further, community values and norms determine which unexpected observations will be taken up into processes of discovery.

As Merton (1948) points out in his description of the "serendipity pattern" in empirical research, the combination of chance and sagacity that leads to a change in theory does so by contributing a "strategic datum" to the epistemic community. Following Achinstein, the kind of datum that contributes to scientific discovery can be described as "potential evidence" (2001). It takes scientific work to produce potential evidence in response to an unexpected observation. Epistemic agents gain epistemic credit for doing that work and thereby contributing potential evidence to a discovery process, even when they do not complete that discovery process, and even when they cannot predict what hypothesis their evidence will ultimately be potential evidence for. Further, serendipity represents a discovery made outside of the methods of normal scientific practice, by chance. Sagacity, therefore, appraises the resourcefulness of a scientist as well as her epistemic skill for producing useful potential evidence.

The case of the triggered memory describes an unexpected observation made during a study in early phase DBS research and the production of potential evidence in response to that observation. This is a case of potential serendipity. A vivid memory experience was triggered unexpectedly by stimulation near the fornix of an obese participant, who was being treated with DBS for his appetite and eating behaviours. The insight, actions and agency of the researchers involved suggest that the observation may result in a serendipitous discovery. However, the probability of serendipitous discovery is increased if the potential evidence produced by that study has collateral value—if it is made available as potential evidence for multiple possible hypotheses.

More specifically, the principle of translational distance (Kimmelman, 2010) suggests that clinical research should progress by making conservative inferences about the generalizability of results, in particular of results from a single case. Minimizing translational distance and attending to collateral value together provide a method for fostering serendipitous

discovery in clinical research. Translational distance provides a method for assessing the likelihood that potential evidence will be taken up by an epistemic community into a process of discovery. That is, translational distance provides a means to prospectively assess the potential value of pursuing the new direction of research inspired by an unexpected observation.

Further, serendipity implies a paradox of control: there are methods for fostering serendipity and for determining whether an unexpected observation is potentially serendipity, but this does not mean that serendipity can be predicted or controlled for. For instance, when the pursuit of potential serendipity entails an ad hoc addition to or change in a research program, following up on an unexpected observation may conflict with the ethics of clinical research. Clinical research is regulated by REBs, who weigh the potential value of the knowledge the trial intends to produce against the risks incurred by study participants. Further, REBs require that fully informed consent be given and maintained by participants, and that the ratio of risk to potential benefit remains favorable. When this ratio changes and there is a chance that the participant may be further harmed than originally intended, a study must be reviewed again by the REB. The same should occur when new epistemic goals are introduced to a research protocol in response to an unexpected observation.

While the requirements for ethical clinical research demand that serendipitous discovery be fostered differently in clinical research than in basic scientific research, this does not necessarily diminish the probability that serendipitous discovery will occur in communities of clinical researchers. Rather, ethical values are some among many values that can either constrain or enable processes of serendipitous discovery. By attending to collateral value and minimizing the translational distance between observations and hypotheses, small steps in clinical research provide the means by which to foster serendipitous discovery without compromising ethics.

7.2 Implications of Conclusions Drawn

7.2.a Implications for Serendipity Theory

Narratives of serendipitous discoveries, properly constructed, will include more than the story of a particular individual who was fortunate and wise. Rather, they will depict a network of relationships, include contingent factors about the world and scientific practice, and call into question the ideal of linear, logical, scientific progress. Such narratives will depict not only the phenomenological experiences of a serendipitous person, but also the social-epistemological factors involved in the making of a serendipitous discovery.

Accounts of serendipity ought to resist perpetuating the idea that sagacity is a kind of personal characteristic, or the mark of a creative genius. Rather, sagacity indicates the wisdom to use scientific methods to produce knowledge whenever opportunity presents. Further, being recognized as sagacious is not the sole responsibility of the researcher, but rather depends on how his epistemic agency is encouraged, supported and perceived by the community. Thus, communities that support the development and exercise of epistemic agency among their members (in part by creating cooperative networks of agents), are likely to benefit from more serendipitous discoveries.

While serendipity is a category used to describe narratives of discovery, narratives of serendipitous discovery will not, when aggregated, provide a consistent profile of serendipitous discovery. Such discoveries will include not only the production of potential evidence, but contingent factors about the context and community that enabled the discovery process and that led to the community appraisal of the individuals and events included. The tripartite definition of serendipity allows for the identification of serendipitous discovery when it has occurred, but both the confluence of the three elements and the construction of a discovery

narrative depend on contingent factors: this identification is both retrospective and potentially unstable. The status of serendipity is dependent on community judgments about agency and value, and these may change over time.

7.2.b Implications for Philosophy of Discovery

Like other narratives of scientific discovery, narratives of serendipitous discovery are constructed retrospectively. Retrospective accounts of a discovery give us the reconstruction of events and the recognition of the agency of individuals involved, but not necessary and sufficient conditions for discovery. The minimal condition for a scientific discovery in response to an observation, including but not exclusive to serendipitous discovery, is the production of potential evidence.

Producing potential evidence is not a purely epistemic activity. It also includes awareness and strategic handling of social-epistemological conditions that reflect the values of epistemic communities and the roles of epistemic agents who are members of those communities. In particular, epistemic agency is illustrated by the successful dissemination of potential evidence so that evidence can be taken up by a community.

Further, serendipity is not a condition for revolutionary science, but an illustration of how discovery arises out of the normal practice of science. Rather than progress through leaps and bounds, the fact that serendipity has led to major discoveries in science attests to the efficacy of conservative approaches to scientific progress.

The content of the 'insight' involved in serendipity is that an unexpected observation is worthy of following up to produce potential evidence. What is worthy of following up in turn is given by the context in which a discovery may be made. That is, what an epistemic community will value sufficiently to take up into a process of discovery is worth changing one's research

direction to follow up. Because discovery processes can take more than one community to complete, the person who has the insight does not always see it proven correct.

Communities can foster the perception, valuing, and uptake of unexpected observations into processes of discovery. They can do this because serendipity happens at the level of the community.

7.2.c Implications for Ethics in Clinical Research

Contemporary research ethics and the regulation of clinical research emphasise the assessment of design. The capacity for taking advantage of unexpected opportunities can be incorporated into design, but only to a limited extent: serendipity remains unexpected, by definition. Further, in fields of research where considerable ignorance remains and uncertainty is great, chance plays a greater role. In order to maximise the epistemic value of early phase trials and the use of advanced technologies, serendipity and other opportunities for discovery should be fostered.

Incorporating collateral value as an endpoint for early phase trials is one way to foster serendipity in early phase research—adding "piggyback" studies to clinical research or practice is one way to incorporate further collateral value. Equally important as increasing the quantity and quality of potential evidence, however, is making that potential evidence available to an epistemic community. Therefore, another method for fostering serendipity is to publish case reports, record and disseminate additional data, and make negative results available. Expanding the scope of potential evidence available to members of communities will result in greater uptake of that evidence, and thereby an improved probability that potential evidence gained unexpectedly will result in a serendipitous discovery.

This production of potential evidence, however, to be ethical, must be regulated as clinical research and subject to the standards of clinical research ethics. The actions required to produce potential evidence and contribute to a serendipitous discovery include justifying the inference one has made about the significance of the original observation, finding and making explicit a meaningful connection between that observation and current knowledge, and preparing and disseminating that evidence so that the epistemic community can take it up and put it to use.

Because ethics does constrain the ability of researchers to follow up on unexpected but significant observations when they are made in human participants, it may seem that serendipitous discovery is itself constrained by the ethics of clinical research. I have shown here, however, that this is not necessarily the case. A research community that shares knowledge, works in cooperative networks, and attends to opportunities for collateral value will foster serendipitous discovery more than a community that emphasises individualistic freedom or competition. As a value held by the epistemic community of clinical researchers, ethics guides the decision-making about which unexpected but significant observations to pursue, when and how, but it does not have to limit the number or value of serendipitous discoveries made.

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