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Varieties of Exploratory Experiment

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Varieties of Exploratory Experimentation in Nanotoxicology

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Abstract: There has been relatively little effort to provide a systematic overview of different forms of exploratory experimentation (EE). The present paper examines the growing subdiscipline of nanotoxicology and suggests that it illustrates at least four ways that researchers can engage in EE: searching for regularities; developing new techniques, simulation models, and instrumentation; collecting and analyzing large swaths of data using new experimental strategies (e.g., computer-based simulation and "high-throughput" instrumentation); and structuring an entire disciplinary field around exploratory research agendas. In order to distinguish these and other activities more effectively, the paper proposes a taxonomy that includes three dimensions along which types of EE vary: (1) the aim of the experimental activity, (2) the role of theory in the activity, and (3) the methods or strategies employed for varying experimental parameters.

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1. Introduction

Although the details of experimental practice received little attention from historians and philosophers of science throughout much of the twentieth century, it has become a topic of much interest during recent decades (see e.g., Gooding, Pinch, and Schaffer 1989; Heidelberger and Steinle 1998; Radder 2003; Rheinberger 1997). One strand of this renewed interest involves the suggestion that experimentation is often of an "exploratory" character rather than just a tool for testing well-formulated theories or hypotheses (Burian 1997; Steinle 1995, 1997; Sargent 1995a, 1995b). This paper examines contemporary research in nanoscale science and technology as a new case study that provides further insights about the nature of exploratory experimentation (EE). Nanotechnology, which involves the manipulation of matter at the molecular scale, is currently receiving major investment in the United States and around the world (Johnson 2004; Keiper 2003).[1] One element of this research activity is the design of nanoscale particles (i.e., roughly 100 nanometers or less in diameter) that can be incorporated into applications as diverse as transparent sunscreens, stain-resistant pants, and longer lasting tennis balls (Royal Society 2004). Because these nanoparticles often

[*] I am grateful to Dick Burian, Maureen O'Malley, and Ken Waters for their help in developing the ISHPSSB session at which the papers in this issue were originally presented. They, along with an anonymous referee, also provided very helpful feedback on earlier drafts of this paper. I thank Tara Sabo-Attwood for clarifying technical aspects of nanotoxicology research, and I appreciate helpful comments by Paul Griffiths, Hans-Jörg Rheinberger, and Chris Toumey based on presentations of the paper.

[1] The term 'nanotechnology' stems from the fact that the atomic scale is in the range of a billionth of a meter, which is called a nanometer. A nanometer is roughly the length of ten hydrogen atoms laid next to each other.

have properties that are different from those that are characteristic of bulk materials, the field of nanotoxicology has arisen in an effort to characterize the biological and environmental effects of these particles.

One of the most prominent nanotoxicology researchers, Gunter Oberdörster, recently led a working group that laid out a screening strategy for investigating the toxicological properties of nanoparticles. The present paper examines Oberdörster's screening plan with the goal of accomplishing two tasks. First, it argues that this screening strategy constitutes a fruitful case study that supplies numerous contemporary examples of EE. In fact, it illustrates so many forms or varieties of EE that it raises questions about how these experimental practices relate and compare with one another. Therefore, the paper's second goal is to suggest a taxonomic scheme for categorizing the varieties of EE in a systematic fashion. To my knowledge, this is the first attempt to provide a systematic analysis of the various forms that EE can take. Sections 2 and 3 provide an overview of current research on exploratory experimentation and on nanotoxicology, respectively. Section 4 then analyzes how current research in nanotoxicology illustrates EE, and Section 5 develops my proposed taxonomy.

2. Exploratory Experimentation

Friedrich Steinle has recently published a number of articles that describe what he calls "exploratory experimentation" (see e.g., Steinle 1995, 1997, 2002). Many of his case studies come from eighteenth and nineteenth century research on electromagnetism. Based on the work of Ampere and others (including Dufay, Faraday, and Goethe), Steinle proposes a description of EE that appears to include at least four major characteristics (although he does not specifically number these characteristics in his own work). First, he claims that "the most prominent characteristic of the experimental procedure is the systematic variation of experimental parameters" (2002, 419). Second, the experimenter aims to formulate empirical regularities, often of an "if-then" character, on the basis of this variation in experiments. Third, Steinle strongly emphasizes that the successful formulation of these regularities frequently requires the revision of existing concepts or the formation of new ones. Finally, he suggests that exploratory experimentation often includes the attempt "to develop experimental arrangements that involve only the necessary conditions for the effect in question and thus represent the general regularity or law in a most obvious way" (2002, 419). In other words, it involves developing an optimal experimental setup for exhibiting the regularity, which might otherwise be fairly elusive or difficult to observe.

A number of other authors have also begun to study the sorts of experimental practices that Steinle has highlighted. Richard Burian (1997) provides a strikingly similar account of EE in his analysis of Jean Brachet's nucleic acid research. Burian emphasizes that Brachet and his co-workers tried to *vary* normal cellular operations in an effort "to find *correlations* between the presence of nucleic acids at particular times and places and the ensuing biochemical, physiological, and morphological changes…" (Burian 1997, 42, italics added). In his contribution to the present journal issue, Burian argues that this sort of exploratory experimentation may be particularly crucial to the

field of molecular biology, because of the contingent historical processes through which biological regulatory systems developed.[2] Laura Franklin (2005) also suggests that EE is becoming more and more central to biological research as "high-throughput" methodologies like genomic and proteomic analyses become more readily available.[3] Maureen O'Malley's essay in this journal issue illustrates the fruitfulness of these techniques.

Other writers have pushed the notion of exploratory experimentation in somewhat different directions. While agreeing with the claim that much experimentation is not primarily directed at testing hypotheses, Rose-Mary Sargent (1995a, 1995b) focuses on the role of experiments in the formulation of new techniques and the application of existing methodologies to new contexts. Ken Waters (2004) has argued that large-scale bodies of scientific knowledge, including classical and contemporary genetics, have been structured (at least in part) by exploratory research strategies. In contrast to the received notion that classical genetics was structured by one or more central theories, Waters claims that it was organized largely by systematic approaches for investigating novel processes and phenomena. This is a departure from Steinle's and Burian's original focus on individual experiments, but it shares their focus on research as an exploratory as opposed to a theory-directed activity. Despite all these current studies, however, there has been little effort to develop a systematic overview of the various forms that EE might take.[4] This paper uses a case study of current research in nanotoxicology to help accomplish that task.

3. Nanotoxicology

Nanoscale science and technology encompass a wide range of research activities, all focused on the manipulation of matter in the molecular size range. Much of this effort is part of ongoing work in materials science and chemistry. For example, in the 1980's and 1990's, researchers developed novel carbon structures such as "buckyballs" and nanotubes, which have very promising combinations of strength, weight, and conductivity properties. Nanoparticles (i.e., particles that are less than 100nm in size) of other materials, such as titanium dioxide or iron oxide, are being used or are likely to be used in clear sunscreens, cosmetic products, self-cleaning windows, anti-fogging glass, stain-repellent clothing, and improved athletic equipment (see e.g., Ratner and Ratner 2003; Royal Society 2004). More complex applications of nanotechnology include the development of better pharmaceutical delivery systems, such as the encapsulation of drugs in molecular structures that promote their release in

[2] Similarly, Robert Brandon (1996) suggests that the biological sciences may require more descriptive work than fields like physics, because there are a greater number of contingent parameters to measure.
[3] Franklin sometimes also uses the term "wide instrumentation." The distinguishing feature of wide or high-throughput instruments is that they "allow the simultaneous measurement of many features of an experimental system" (Franklin 2005, 888). A good example is a DNA microarray, which allows investigators to compare the expression of thousands of a cell's mRNA sequences at once.
[4] Steinle and Franklin have tried to distinguish between different forms of EE in their previous work. O'Malley also provides some valuable reflections on the relationship between EE and other forms of experimentation in her accompanying essay. The present article tries to provide a somewhat more complete and systematic account of the ways in which different forms of EE compare with one another.

particular tissues. Nanotechnology may also revolutionize energy technology if, for example, it facilitates the production of more effective solar panels and fuel cells.[5]

Much of the current excitement regarding nanotechnology stems from the possibility of producing nanoparticles that display unique properties as a result of their exceptionally high surface area and their potential for displaying quantum effects (Royal Society 2004). These unique properties also make it difficult to predict their toxicological characteristics, however, which has spawned the development of "nanotoxicology." Preliminary research in this field suggests that nano-based materials may have a variety of worrisome characteristics, including: increased ability to pass through cells, tissues (perhaps even the skin), and the blood-brain barrier; potential to interfere with proteins (because nanoparticles and proteins have similar sizes); and the possibility of carrying other toxic substances along with them (Oberdörster et al. 2005; Royal Society 2004). Some studies have in fact found that nanoparticles of various sorts can cause inflammation, oxidative stress, structural damage, and cell death in tissues that include the lungs, kidneys, and brain (see e.g., Balbus et al. forthcoming; Colvin 2003; Oberdörster 2004; Oberdörster et al. 2005). Building on previous work concerning the health effects of ultrafine particles in air pollution, researchers are now attempting to determine the variables that influence the toxicity of nanomaterials.

In 2005, an expert working group led by Gunter Oberdörster published a paper summarizing the elements of a screening strategy for identifying hazards from nanoparticles (see Oberdörster et al. 2005). The report provides an excellent overview of the sorts of research strategies that nanotoxicologists are currently employing. It calls for three major categories of research: (1) variation and measurement of a wide variety of particle characteristics; (2) *in vitro* studies of the effects of these particles on multiple tissue types; and (3) *in vivo* studies of the effects of the particles in multiple animal models. With respect to the first element of research (i.e., variation of particle characteristics), the strategy suggests measuring dose concentration (measured in surface area or the number of particles and not just in mass), size distribution, shape, composition, surface chemistry, surface contamination, surface charge, crystal structure, particle physicochemical structure, agglomeration state, porosity, method of production, preparation process, heterogeneity, and prior storage of the material. Moreover, the report recommends that these variables be measured, if possible, not only for the supplied particles but also when they are administered and after they have been taken up in the *in vitro* or *in vivo* experimental system (Oberdörster et al. 2005).

Measurement of this range of variables is of crucial importance, because researchers are currently not sure which particle characteristics are most predictive of toxicological properties. For example, toxicologists have traditionally found that the toxicity of an administered substance is roughly proportional to its dose (measured in terms of mass concentration), regardless of the size of the administered particles. It has

[5] This paper does not consider the more dramatic and controversial applications envisioned for nanotechnology, which include the possibility of "downloading" the contents of the human brain into computer systems or the creation of nanoscale robots with nearly unlimited manufacturing capabilities (see e.g., Drexler 1986; Keiper 2003).

been surprising for nanotoxicologists that this regularity may not hold for the toxic effects that they study. They have discovered that decreasing the mass concentration of a particular nanomaterial can still result in the same or even increased toxic effects if the surface area of the administered material increases (e.g., via administration of a greater number of smaller particles). In other words, the mass of nanoparticles may be much less important to predicting toxicity than their size and surface area. Therefore, one of the major goals of Oberdörster's screening plan is to determine which particle characteristics are most important to consider when predicting the toxic effects of nanomaterials.

The second element of the screening strategy consists of *in vitro* studies of a very wide range of targets, including numerous cell types within the lung, multiple skin assays, and multiple organs and organ systems (e.g., spleen, liver, blood, nervous system, heart, and kidney). Just as the first element of the screening plan is designed to determine which variables are most predictive of toxic effects, this second component is designed to determine whether there are specific tissues or biological endpoints that are most likely to be affected by particular nanomaterials. It is especially interesting from the perspective of this paper that this second element of the Oberdörster report includes the application of four approaches associated with "computational toxicology," which is defined as "the application of mathematical and computer models and molecular biology approaches to improve prioritization of data requirements and risk assessments for environmental protection" (Oberdörster et al. 2005; see also Balbus et al. 2007).

The first of these four approaches, computational chemistry, uses simulation techniques to model molecular structures and predict their properties. The second and third approaches, molecular biology and bioinformatics, use genomics and proteomics to develop databases that can assist in identifying nanomaterials that produce toxic effects. For instance, these techniques can enable researchers to compare the gene expression patterns in tissues exposed to nanoparticles versus those in control tissues. If significant genes (such as those associated with inflammation responses) are upregulated in the tissues exposed to particular nanomaterials, it suggests that those particles may have toxic properties. The fourth approach, systems biology, involves the use of mathematical modeling to predict how toxic effects in specific tissues or organisms will affect broader biological systems. The report acknowledges that it will still be some time before computational toxicology is able to predict the relationships between particle structure and toxicity in any detail, but it suggests that the results of *in vitro* research should be employed to facilitate the development of these computational approaches.

The third, *in vivo*, element of the screening strategy involves analyzing the effects of nanoparticle exposure via pulmonary, oral, dermal, and injection routes. The *in vivo* effects to be studied include a variety of markers for damage and oxidative stress as well as cell proliferation. Like the second component of the screening strategy, these studies are designed to uncover relationships between nanoparticle characteristics and their biological effects. Because of evidence that nanoparticles have a greater ability to move throughout the body than larger particles, the report calls for special *in vivo*

studies designed to identify subtle effects that are remote from the source of exposure. These studies include: analysis of particle deposition, translocation, and biopersistence; investigation of effects on the reproductive system; examination of effects in compromised animal models; and use of genomic and proteomic analyses to highlight risks that might not be obvious based on other experimental methods.

4. Nanotoxicology as Exploratory Experimentation

This section's goal is to examine the three-part nanotoxicology screening strategy as a fertile case study of EE, thereby facilitating the development of a systematic taxonomy.[6] The most obvious illustration of exploratory activity in the nanotoxicology case is the variation of experimental parameters to identify particle properties that are predictive of toxic effects. This is the sort of exploratory activity that most resembles what Steinle described in his seminal papers on EE. Researchers are forced to examine an extremely wide variety of particle characteristics, because they are not sure which ones will turn out to be most predictive of toxicity. Moreover, they have to investigate potential effects on a wide range of organ types and biological endpoints, because they are not sure which ones are most likely to be affected by particular sorts of nanoparticles. As a consequence of this exploratory research, investigators hope to uncover a list of variables that *do* and that do *not* significantly alter the toxicity of nanomaterials.

A second way in which EE permeates nanotoxicology is illustrated by researchers' efforts to develop standardized protocols and reproducible effects. Scientists working at the nanoscale have to engage in a good deal of exploratory research in order to make effective toxicological experiments possible, because the capability to produce particles with precise characteristics and the ability to measure those characteristics is currently incomplete. In other words, the nanotoxicology experiments that are designed to vary parameters and identify regularities depend on a great deal of "background" experimentation that seeks to establish protocols, design instruments, and produce particles with reproducible features. Much of this background research remains implicit in Oberdörster's article (2005), but the report from another recent workshop (Balbus et al. 2007) has heavily emphasized the need for improved methodologies in nanotoxicology. For example, it pointed out the value of having relatively quick and easy *in vitro* assays or screening techniques for identifying potentially hazardous nanoparticles, but it concluded that these methodologies are insufficiently developed at present. The one sort of "background" or "methodological"

[6] One might object that, because toxicology experiments have a well-planned structure and include a clear conception of what the investigators are looking for (namely, toxic effects of various sorts), they do not count as genuine instances of EE. An initial response to this worry is that, even in Steinle's classic case studies, the investigators sometimes had a fairly clear sense of the phenomena that they were looking for (such as production of an electric current via the motion of a magnet); the experiments were still exploratory in the sense that the researchers were unsure of the major regularities that described when and how those phenomena of interest would occur. A second response is that, as this paper emphasizes, EE comes in many varieties, so it seems unhelpful to exclude the exploratory activities associated with nanotoxicology just because they fail to have some of the characteristics that other instances of EE may have.

research that Oberdörster and his colleagues (2005) explicitly recommend is the use of *in vitro* toxicology results to help design more effective computational simulations. Johannes Lenhard (2007) has previously argued that the process of developing simulation models is often exploratory, requiring an iterative process of altering models in response to experimental findings.[7]

It may be fruitful to distinguish a third form of EE, which is also illustrated by computer-based simulations, as well as by the genomic and proteomic assays that Oberdörster and his colleagues (2005) recommend under their category of "computational toxicology." Whereas Lenhard emphasizes that exploratory work is involved in *developing* simulation models, other analysts emphasize that one can *use* these simulations as tools for conducting exploratory work. Simulation models and various forms of "high-throughput" instrumentation facilitate experimental activities that are somewhat distinct from other forms of EE in that they generate particularly large quantities of data that researchers can subsequently analyze in search of patterns. Consider this quotation from an article by Eric Winsberg:

> If they [i.e., simulationists] want to discover functional dependencies [i.e., regularities], then they must also run a barrage of trials, looking at the results across a wide range of parameters. It is without a doubt this aspect of simulation that carries the most obvious methodological characteristics of experimental work. (2003, 111)

The use of simulation in nanotoxicology may ultimately fit Winsberg's description very well; toxicologists hope to develop sufficiently realistic simulations so that they can vary a range of parameters and identify regularities between particle characteristics and particular toxic effects. Similarly, the Oberdörster screening plan recommends various forms of genomic and proteomic analyses in the hope that researchers can sift through large bodies of data regarding the levels of various genes and proteins expressed in tissues that are exposed to specific sorts of nanoparticles. The goal is to identify specific nanoparticle characteristics that tend to result in significant biological responses, which might be difficult to identify without information about these gene and protein expression patterns.

Finally, if one takes a step back and considers the principles that structure nanotoxicology as a research field, it appears to support Waters's (2004) contention that bodies of knowledge can be organized by investigative strategies that are exploratory. As Section 5 will discuss more fully, Waters claims that classical genetics was not structured primarily by the goal of testing the fundamental principles of genetics but instead involved using those principles to assist in gathering information about a range of other phenomena. This may be a fourth way in which EE is present both in nanotoxicology and in traditional toxicological research. It seems clear that toxicology

[7] In a currently unpublished paper entitled "Structural Underdetermination in Simulation Modeling," Lenhard distinguishes two aspects of simulation models: a structural and a specification component. He argues that general model structures, such as cellular automata (CA) models, are incomplete in that they have to be specified for particular applications by adjusting variables, parameters, and modules. He suggests that this specification process may involve a good deal of exploratory work, which arguably has much in common with EE.

research does not normally involve a continual effort to *test* paradigmatic theories, such as the principle that toxic responses vary with dosage. Instead, toxicologists *use* the dose-response relationship as a *means* for systematically investigating the toxic effects of various substances and organizing the resulting data. Thus, the field of toxicology may itself be organized around systematic exploratory efforts. Nanotoxicology maintains the same exploratory characteristics, but it incorporates additional elements of EE because it is not even clear that the dose-response relationship of traditional toxicology is the most appropriate guide to this area of research. Nanotoxicologists are currently seeking for comparable regularities that can then organize their subsequent studies.

It is clear, therefore, that the Oberdörster screening strategy provides a rich case study to illustrate EE in contemporary research. I have suggested in this section that it may be fruitful to distinguish four sorts of exploration occurring in this case: variation of experimental parameters to identify regularities; exploratory development of new techniques, simulation models, and instrumentation; use of new strategies (e.g., computer-based simulation and high-throughput instrumentation) to generate large quantities of data and search for patterns; and organization of the entire disciplinary field around exploratory research agendas. The richness of this case raises some difficult questions about exploratory experimentation, however. How do these various sorts of exploration relate to and compare with one another? Should they all be labeled as "exploratory experimentation"? Is there a continuum between "exploratory" forms of experimentation and other forms, or is there a sharp separation between them?[8] What are the necessary conditions for a form of experimentation to be labeled "exploratory"? How many varieties of EE might there be? What criteria serve best for differentiating those varieties? How does the sort of exploratory experimentation analyzed by writers like Steinle and Burian compare to other varieties of EE?

In the early stages of research on EE, these questions were not as pressing, because the major goals of the science studies community were to show that there *was* such a thing as exploratory experimentation and to sketch some of its major characteristics. But now, as the importance of EE becomes more generally accepted and as case studies such as this one highlight its complexity, it would be helpful to start developing a systematic taxonomy of the *varieties* of exploratory experimentation. Section 5 turns to this task.

5. A Taxonomy of Exploratory Experimentation

The nanotoxicology case study has highlighted the fact that there may be a variety of scientific activities that are related in at least some way to the notion of exploratory experimentation. The challenge that one immediately faces in developing a taxonomy of these activities is how to develop a principled set of categories or

[8] Some of these questions are starting to receive attention. For example, Brandon (1996) has suggested that the difference between experimental studies that test hypotheses and those that do not is one of degree rather than a sharp difference in kind. Burian's and O'Malley's contributions to this journal issue also help to address these sorts of questions.

dimensions for organizing them. The remainder of this paper suggests one scheme that seems to be promising and then fills it in with examples from the nanotoxicology case study and other examples of experimental work. Although it is surely not the only reasonable system that one might develop, it has the advantage of being based on what I take to be the most fundamental, uncontroversial features of EE. The taxonomy starts with the observation that all the authors who discuss this form of experimentation seem to be reacting against previous philosophical literature that regarded experimental work primarily as a tool for testing theories. Thus, from a *negative* perspective, the most fundamental characteristic of EE seems to be that it, in contrast to other types of experimentation, does *not* serve the aim of testing theories or hypotheses. The central *positive* feature of EE follows from this negative one. Because EE does not involve testing specific predictions of a particular theory, there is a "looseness" in its structure that allows for, and encourages, variation in the experimental data collected.

In order to avoid begging questions about the nature of EE, therefore, the taxonomic scheme developed here starts with these two fundamental characteristics: (1) it does not aim to test theories, and (2) it involves extensive variation of experimental parameters.[9] These two features suggest two dimensions along which the varieties of EE can vary. First, if EE does *not* have the aim of testing theories, then one can distinguish various types of EE according to the range of *positive* aims that they *do* have. Second, if EE involves extensive variation of experimental parameters, one can arrange the kinds of EE according to the key methods or experimental strategies used for varying these parameters. One could stop with these two dimensions, but I would like to suggest one more dimension that flows from the first characteristic of EE. The first feature is that EE does not involve *testing* theories, but it does not state that theories have *nothing* to do with EE. Given the prominent role that the philosophy of science has traditionally given to scientific theorizing, it may also be fruitful to distinguish varieties of EE based on the role that theory plays in them. Thus, I propose a taxonomy that varies along three dimensions:

(1) The positive aim of the experimental activity;
(2) The role that theory plays in the experimental activity;
(3) The methods or strategies used for varying parameters.

According to this taxonomy, then, one can characterize a particular variety of EE by specifying what its positive aim is, what role theory plays in it, and what methods are employed for varying parameters. We will see that these dimensions appear to be at

[9] Those who suggest additional characteristics of EE can then *either* argue that all experimentation that has these two characteristics also has the additional characteristics, *or* they can argue that they are interested in a particular sort of EE that has those additional features. Alternatively, one could argue that I have defined EE too broadly and insist that the label 'exploratory experimentation' should be reserved for experimentation that has some additional characteristics. Whether or not one agrees with this suggestion, I do not think that it takes away from my project. Even if one were to reserve the EE label for a subset of the sorts of experimentation that have the two characteristics identified here, it is still arguably important to consider the full range of experimental activities that do not involve theory testing (and that have therefore been neglected in previous philosophical literature). Those who want to use the EE label in a narrow sense could regard this paper as an attempt to provide a taxonomy of a "family" of neglected sorts of experimentation, of which EE is a subset. In what follows, however, I will use the EE label for this entire family of experimental activities.

least partly independent of one another; for example, the positive aim of the experimental activity need not always determine the role that theory plays in it or the methodology used for varying parameters. The remainder of this section briefly sketches some major ways that varieties of EE can vary along these three dimensions (see Figure 1), drawing both from the nanotoxicology case study and from previous literature on scientific experimentation.

Dimension 1: Aims of the Experimental Activity

The most obvious goal of exploratory experimentation (i.e., identifying major regularities between variables and developing a corresponding conceptual scheme) has already been well characterized by Steinle, so this section considers some alternative aims. Richard Burian has emphasized that researchers often use EE to stabilize and characterize particular entities in time and space, which involves a somewhat different focus than the identification of regularities. For example, in disciplines such as organic chemistry or molecular biology, researchers often vary the parameters of their experiments in an effort to synthesize or purify or characterize phenomena more effectively. Identifying the mechanisms that produce a phenomenon may be another aspect of this experimental activity (see e.g., Machamer et al. 2000). Michael Heidelberger (2003) has distinguished several different forms that this aim of EE might take. He suggests that it sometimes involves a *productive* use of instrumentation to "produce phenomena that normally do not appear in the realm of human experience" (2003, 146). In other cases, it involves a *constructive* use of instrumentation, which may involve the production of phenomena in a "pure form" or the manipulation of phenomena in desired ways. This constructive activity is also arguably found in Steinle's cases, when researchers attempt to exhibit regularities in a particularly perspicuous way. Finally, *imitative* forms of experimentation attempt to "produce effects in the same ways as they appear in nature without human intervention" (2003, 147).

As mentioned earlier, Sargent (1995a, 1995b) has previously emphasized another possible goal of EE, namely, to develop new experimental techniques, instrumentation, or simulations. Initially, this may involve varying multiple design elements of an instrument to determine which design will be most effective (Rothbart 2003). Even after creating effective instruments, Rainer Lainge emphasizes that scientists have to engage in an extensive exploratory process of "pretesting" to determine what conditions are needed in order to get any experimental results at all (2003, 134-135). Sargent argues that exploration also occurs when scientists apply established experimental techniques to novel situations. Moreover, we have encountered Lenhard's (2007) claim that iterative, exploratory work is often involved in developing effective computer simulation models. Thus, a number of authors are starting to emphasize that EE of the sort that creates instrumentation, simulations, and effective experimental protocols is necessary in order to make EE of the sorts described by Steinle and Burian possible. This sort of preliminary EE plays an important role in the nanotoxicology case study, because researchers are attempting to develop improved

instrumentation and techniques for synthesizing and characterizing nanoparticles with particular physical and chemical characteristics.

The nanotoxicology case suggests that exploratory experimentation may sometimes have yet another aim, that of resolving scientific anomalies. We have seen that at least some nanoparticles fail to display the sorts of dose-response relationships (based on mass concentration) that play a paradigmatic role in traditional toxicology research. Lindley Darden has suggested that researchers respond to anomalies via a series of steps, the first two of which involve: (1) confirming that the anomaly exists, and (2) localizing it within a particular component of a theory (1991, 269). I have previously argued that these early stages of anomaly resolution cannot always be reduced to the repetition of a few experiments (Elliott 2004, 186). Instead, researchers may have to pursue a variety of strategies, including the exploratory approaches of examining which variables affect the anomalous results, looking for evidence of the anomaly under diverse conditions, and searching for mechanisms that might produce it (Elliott 2004, 188). In the nanotoxicology case, researchers appear to be pursuing a number of these strategies to determine how traditional toxicological paradigms may need to be revised in response to their new findings.

Dimension 2: Role of Theory in Guiding the Experimental Activity

A second dimension along which the types of EE can vary is the role of theory in guiding the experimental activity. Steinle's classic examples of EE (specifically, explorations of electromagnetic phenomena) involved cases where experimentalists were working with a bare minimum of theoretical influence. One might compare these cases to Thomas Kuhn's descriptions of pre-normal science, in which researchers have no widely accepted paradigm to guide their investigations (Kuhn 1970). The precise extent to which theory is absent in these cases is, admittedly, a matter of debate. Heidelberger has argued that experimental cases like those described by Steinle need not be theory laden, at least insofar as they need not be theoretically interpreted in what he calls a Duhemian sense (2003). Others have questioned the extent to which one can actually deny the theory ladenness of experimental results, even in cases that seem to involve minimal theoretical interpretation (see e.g., Carrier 1998; Radder 2003). At any rate, it is surely possible to distinguish experiments that are more or less heavily influenced by theory than others, and Steinle's examples seem to involve the bare minimum of theoretical involvement. It is important to remember, however, that although Steinle's preferred form of EE includes very little role for theory in the *design* or *guidance* of EE, the *goal* of the activity is to develop new theoretical ideas and concepts.

Other varieties of EE draw somewhat greater guidance from scientific theory. In her recent article, Franklin emphasized the distinction between theoretical background knowledge versus local theories that experiments are designed to test or explore (2005, 891). She provides examples from contemporary biology of experiments designed to examine vast numbers of genes in the hope of identifying some that play important regulatory roles in the yeast cell cycle. She explicitly distinguishes

experiments like this one from those discussed by Steinle, because she claims that her biological experiments are informed by much more extensive theoretical background knowledge (e.g., about the nature of the cell cycle and the role of genes in that process) (Franklin 2005, 893). Nevertheless, she insists that these biological experiments should still be regarded as exploratory insofar as they do not involve the testing or analysis of a specific, local theory (see also Sargent 1995b). As in Franklin's case studies, background theory plays an important role in the development and interpretation of the computational toxicology approaches (e.g., computer simulation and genomic analyses) that Oberdörster and his colleagues are recommending.

The nanotoxicology case study suggests a third characteristic of some EE, in which theory plays the role of a starting point or a "foil" in the exploratory process. Theory seems especially likely to play this role when EE has the aim of resolving anomalies. For example, much of the exploratory experimentation in nanotoxicology seems to be designed to figure out precisely what has gone wrong with the old paradigm (which specified the important variables that affected toxicity) and to determine how it may need to be altered or elaborated in order to resolve anomalous findings. Thus, whereas Steinle's variety of EE resembles Kuhnian prenormal science, forms of EE where theory plays this role are more akin to Kuhnian puzzle solving or (if problematic findings cannot be easily resolved) revolutionary science. In other words, this sort of exploratory research involves collecting a wide range of data in hopes of determining how, if at all, a particular theory has gone wrong or how it applies in a somewhat new context. In some cases, this activity may be comparable to Kuhn's (1970) description of normal science as a process of articulating theories that need to be elaborated and specified.

Finally, Waters's recent article (2004) on exploratory experimentation in classical genetics illustrates a fourth possible characteristic of EE, in which instructions or strategies for exploration actually play something like the traditional role of "theory" in a particular domain. In cases of EE that display this characteristic, exploration plays a fundamental role in structuring scientific disciplines and bodies of knowledge (much like what scientific theories would do in other disciplines) rather than being only a characteristic of particular experiments. For example, Waters argues that classical genetics from the 1920's to the 1940's included three major cognitive elements: pools of special knowledge, patterns of explanation, and patterns of investigation. The third element, "patterns of investigation," consisted of exploratory strategies that structured research. According to Waters, researchers guided by these strategies designed series of experiments such that explanations of the results, explanations which typically appealed to the transmission theory of inheritance, would reveal information about one or another biological process (and often processes not related to the transmission theory).

Consider Waters's example of "genetic analysis." He claims that it was a crucial investigative tool of classical genetics, whereby researchers identified the alleles responsible for a mutant phenotype, pinpointed them to particular chromosomes, and determined whether they were alternative forms of any previously known genes. By doing so, the investigators learned about the processes that had been mutated (2004,

793). While critics might claim that the ultimate goal of these investigative or exploratory strategies was further *explanatory* knowledge of biological processes, Waters points out that classical genetics was still structured by the *investigative* strategies and not the explanatory knowledge that they did not yet have (2004, 792). Moreover, even if each individual experiment recommended by these investigative guidelines was not precisely exploratory in the senses described by Steinle or Burian, the overall collection of experiments was arguably exploratory insofar as it was designed to uncover a range of information about phenomena that were not well understood. We saw in Section 4 that the disciplines of nanotoxicology and toxicology in general also appear to be structured by exploratory programs for research.

Dimension 3: Methods or Strategies for Varying Experimental Parameters

Finally, one can uncover a rich diversity of EE by examining the different methods or strategies that scientists use for varying experimental parameters. Steinle's classic cases of EE involved individual experimenters who varied the parameters of their experiments in fairly straightforward ways (e.g., testing different substances, altering the structure of the experimental apparatus, and so on). With the goal of distinguishing different varieties of EE, one can see that some of the experimental activities described by Burian involve a somewhat different approach to varying experimental parameters. Burian emphasizes that Brachet and his coworkers used multiple experimental techniques and instruments to characterize and isolate particular entities and phenomena (1997). Thus, this variety of EE is not so much a matter of systematically altering the features of an experiment in order to uncover regularities (as in Steinle's cases) as an attempt to study a phenomenon using as many tools and techniques as possible so as to understand it more fully and to gain more solid epistemic access to it.

Franklin's article (2005) highlights another important way to vary experimental parameters. She emphasizes that much of biological science is now being transformed by the use of high-throughput instrumentation, such as genomic microarrays, proteomic analyses, and fMRI scans (see also O'Malley this issue). These techniques allow scientists to collect very large amounts of data concerning a particular experimental system at once. Franklin argues that these tools, in conjunction with adequate computing power to analyze the results, encourage the pursuit of exploratory experimentation, because they allow scientists to gain useful information even if they are not initially sure exactly what to look for or where to look (2005, 898). Therefore, insofar as the choice of instrumentation encourages different sorts of experimental practices, it may advance our understanding of EE to distinguish exploratory work with high-throughput instrumentation from exploratory activities with more traditional instrumentation.

The nanotoxicology case study also highlights a fourth way of varying experimental parameters to facilitate EE, namely, working as a community to collect experimental results under a wide variety of conditions. Toxicology experiments are sufficiently long and expensive that individual investigators cannot, as *individuals*,

perform a very broad range of experiments with varying parameters. Nevertheless, different toxicologists are performing experiments using nanoparticles that incorporate a range of physical and chemical characteristics, and they are testing effects on different animal models and endpoints and tissue types. The net result is that, as a *community*, they are engaging in exploratory activity that will hopefully enable them to identify the crucial factors that determine nanoparticle toxicity.

Finally, a fifth strategy for varying experimental parameters is to move from traditional, physical experiments to various forms of modeling and simulation. One approach of this sort is to develop physical models of the phenomena under investigation and to vary the characteristics of those physical models. Perhaps the most famous example of this activity is Watson and Crick's effort to uncover the structure of DNA by manipulating models of its chemical building blocks (Judson 1996). Another step beyond the use of physical models is to develop computer-based simulations of phenomena, thus enabling investigators to explore with relative ease the consequences of varying initial conditions and experimental parameters. Mary Morgan explicitly refers to some of these simulation approaches as "exploratory" (2003, 226; see also Keller 2003), and she clarifies that they can range from "pure" simulations to ones that incorporate physical models in a number of different ways. Although simulation techniques still require much improvement in the domain of toxicology, Oberdörster and his coworkers recommend that they be pursued further in the future (2005). These simulation approaches also occasionally bear similarities to thought experiments (Morgan 2003, 218), which might constitute a particularly abstract form of EE in some cases. For example, Rothbart (2003, 246) argues that thought experiments play an important role in the exploratory design of new instrumentation.

Application to the Nanotoxicology Case

We can now use this taxonomy to clarify the range of ways that exploratory experimentation is occurring in the nanotoxicology case and to compare this activity with other descriptions of EE. To place a particular sort of exploratory experimentation within the taxonomy, one can identify where it fits along each of the three dimensions. Consider, for example, Steinle's influential case studies of electromagnetic research (see e.g., Steinle 1995, 1997, 2002). The aim of experimental activity in those cases was to identify regularities and to develop new concepts. The role of theory in these experiments was quite minimal; the investigators frequently had almost no formal background theory to guide their investigations. The method for varying parameters generally involved working as individuals, varying the elements of an experimental setup. Thus, the taxonomy highlights the fact that, while Steinle has uncovered a particularly striking variety of exploratory experimentation, it occupies just one particular location in a three-dimensional space that includes many other possibilities.

Scanning the three dimensions of the taxonomy highlights some of the alternative characteristics of EE in the nanotoxicology case. One of the most striking consequences of viewing this case study from the perspective of the taxonomy is that it makes the experimental activity in this case appear not so much like four distinct sorts

of EE (as one might think based solely on the analysis in Section 4) as like a complex tapestry of exploratory activity that incorporates a rich variety of characteristics. For example, whereas Section 4 distinguished the search for regularities from the collection and analysis of large swaths of data as two "forms" of exploration, it now appears that the analysis of large data sets is just one among several methods used by nanotoxicologists to identify regularities. Moreover, Section 4 identified the structuring of the entire discipline of nanotoxicology as a separate way in which exploratory activity occurs, but the search for regularities seems more like an effort to facilitate this structuring of the discipline than like a wholly distinct research activity. Therefore, it may be more fruitful to scan the dimensions of the taxonomy with the goal of developing a systematic sense of the characteristics present in the case study rather than trying to separate out multiple entirely distinct sorts of exploratory experimentation. With respect to the first dimension, some of the experimental activity in the nanotoxicology case has the same goal as Steinle described: identifying crucial regularities. Nevertheless, other aspects of the EE in nanotoxicology include somewhat different aims, such as the resolution of anomalous findings or the development of new experimental techniques, simulations, and instrumentation.

Turning to the second dimension of the taxonomy (i.e., the role of theory), the forms of EE described in Section 4 appear to display several characteristics. Whereas background theory played very little role in Steinle's cases, nanotoxicology starts with the dose-response regularities associated with traditional toxicology and employs EE in an effort to determine precisely where they go wrong in this new domain. Background theory also plays a crucial role in the interpretation of genomic and proteomic data, as well as the creation and interpretation of simulations. We have also seen that the entire discipline of nanotoxicology may be structured more by exploratory strategies than by a single, high-level theory. Section 4 suggested that traditional toxicologists already employ the dose-response relationship as a tool for collecting and organizing toxicity data for a wide range of substances, and nanotoxicologists are looking for similar regularities that can structure the collection of toxicity data for nanoparticles.

Turning to the third dimension of the taxonomy (i.e., methods for varying parameters), the forms of EE illustrated by Oberdörster's screening strategy occupy a number of positions along the dimension. Researchers may work as individuals (or as a group in a single laboratory) to vary the elements of their toxicology experiments. However, it is also likely that much of the exploratory work in nanotoxicology will stem not so much from extensive variation of parameters by individual laboratories or investigators as from the combined work of the scientific community. Different investigators will pursue experiments with varying nanoparticles, endpoints, and biological models, resulting in a composite picture that assists toxicologists in determining the fundamental regularities in this new domain of study. Section 4 also described several alternative strategies for varying parameters, including the use of high-throughput instrumentation (e.g., genomic or proteomic analyses) and computer simulations. Thus, the taxonomy developed in this section appears to provide a helpful role in categorizing the multiple sorts of exploratory activity displayed by the nanotoxicology case study.

6. Conclusion

This paper focused on two goals. First, it argued that the systematic nanotoxicology screening strategy recently proposed by Oberdörster and his colleagues exhibits a rich variety of exploratory experimentation. Second, because the relationships between the various sorts of exploratory activities in the case study appeared to be complex, the paper proposed a tentative, three-dimensional taxonomic scheme for conceptualizing varieties of exploratory experimentation. There appear to be multiple benefits to formulating a taxonomy of EE at this time. It may promote a deeper understanding of experimentation in general and the range of characteristics associated with it. It may spur further investigations of some of the experimental activities that appear in the taxonomy but that have not been studied in detail. It may also prevent confusion or conflation of distinct experimental activities that have unique characteristics. Finally, by emphasizing the range of activities that exploratory experimentation encompasses, it places renewed emphasis on the importance of this phenomenon.

After encountering such a wide range of exploratory activities in this paper, however, one might begin to worry that the concept of EE has expanded to include almost all experimental work.[10] This would weaken the significance of exploratory experimentation, which was intended to be a new subject for investigation, one that contrasts with previously studied modes of experimentation that are primarily hypothesis- or theory-driven. Fortunately, it is not hard to find examples of experiments that are primarily non-exploratory; in fact, the most well known experiments in the history of science are generally of this sort. For example, Arthur Eddington's classic eclipse experiments were designed to settle a very precisely specified question, namely, whether the positions of particular stars near the sun were shifted in the manner described by Einstein's General Theory of Relativity or by Newtonian theory. Similarly, one of the most famous experiments in the history of biology, Matthew Meselson and Franklin Stahl's test of the semi-conservative replication of DNA, was designed to evaluate several very specific alternative hypotheses regarding the replication process. One thinks also of the experiments designed to test whether a bright spot is visible at the center of the shadow cast by a circular diffracting screen, or whether the quantity of neutrinos produced by the sun corresponds to the predicted value, or whether quantum particles behave in accordance with Bell's inequalities.

The common characteristic of these non-exploratory experiments is that they are designed with the goal of testing a specific prediction of a particular hypothesis or theory, and thus they are not designed to vary multiple parameters in search of significant phenomena. It seems clear that much experimentation is of this non-exploratory sort. Laura Franklin (2005) quotes contemporary biologists who insist that, although high-throughput instruments are starting to encourage a new breed of more exploratory experiments, biological experimentation has traditionally focused on testing predictions generated by specific hypotheses. Of course, those who come away from

[10] I am grateful to a referee from HPLS for highlighting this point.

this paper with the suspicion that most experimentation is exploratory are still probably correct in a limited sense. Even experiments that are primarily non-exploratory can themselves be embedded in a great deal of exploratory work. For example, the development of instrumentation that can effectively test a particular hypothesis may require a great deal of exploration. As O'Malley emphasizes in her contribution to this journal issue, it would be enlightening in the future to study how researchers integrate both more theory-directed and more exploratory research activities into their experimental practice.

There are at least two other ways in which the present taxonomy could be improved in the future. First, in order to develop a more complete understanding of EE, it is important to consider in more detail how the various dimensions of the taxonomy relate to one another. Although I have suggested that the dimensions are at least partially independent of one another, there are probably interesting relationships between them. For example, it is probably the case that some methods or strategies for varying experimental parameters will serve particular aims of exploratory experimentation more effectively than others. Furthermore, as we saw when applying the taxonomy to the nanotoxicology case, it may be artificial in some cases to distinguish varieties of EE too sharply, pinpointing them to single locations within the taxonomy. Exploratory activities may often incorporate a jumble of different aims, methodological approaches, and roles for theory. A second project is to provide a more exhaustive list of the characteristics that EE can display. The features described here are heavily influenced by the sorts of exploratory activity that are obvious in the nanotoxicology case study and the examples of EE that have been discussed in recent literature. One of the purposes of proposing a preliminary taxonomy such as this one is to encourage others to identify other characteristics of EE that vary along these dimensions or perhaps along other dimensions. Therefore, this taxonomic work hopefully provides a starting point for a range of further investigations.

Figure 1: A taxonomy of the characteristics associated with different kinds of exploratory experimentation, organized according to three relatively independent dimensions or categories.

Dimensions of EE	**Varying Characteristics of EE Within the Dimensions**
Aims of Experimental Activity	Identifying regularities and developing new concepts Isolating or manipulating particular entities or phenomena Developing experimental techniques, instrumentation, or simulations Resolving anomalies
Role of Theory in the Activity	Playing a minimal role relative to other forms of experimentation Providing background information Serving as a starting point or foil Being constituted by exploratory projects or strategies
Methods or Strategies For Varying Parameters	Working as an individual investigator to vary elements of an experimental setup Using multiple experimental techniques to characterize a phenomenon Using "high-throughput" instrumentation to collect large quantities of data Working as a community to design a range of experiments that vary key parameters Developing models and simulations that can vary parameters

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