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The doctrine of specific etiology

Lauren N. Ross[1]

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Abstract
Modern medicine is often said to have originated with nineteenth century germ theory, which attributed diseases to bacterial contagions. The success of this theory is often associated with an underlying principle referred to as the "doctrine of specific etiology". This doctrine refers to specificity at the level of disease causation or etiology. While the importance of this doctrine is frequently emphasized in the philosophical, historical, and medical literature, these sources lack a clear account of the types of specificity that it involves and why exactly they matter. This paper argues that nineteenth century germ theory involves two types of specificity at the level of etiology. One type receives significant attention in the literature, but its influence on modern medicine has been misunderstood. A second type is present in this model, but it has been completely overlooked in the extant literature. My analysis clarifies how these types of specificity led to a novel conception of etiology that continues to figure in medicine today.

Keywords Causation · Biomedicine · Biology · Medicine · Explanation

> *Unquestionably the doctrine of specific etiology has been the most constructive force in medical research for almost a century and the theoretical and practical achievements to which is has led constitute the bulk of modern medicine. Yet few are the cases in which it has provided a complete account of the causation of disease…. In reality…the search for the cause may be a hopeless pursuit because most disease states are the indirect outcome of a constellation of circumstances rather than the direct result of single determinant factors* (Dubos 1959, 102).

✉ Lauren N. Ross
rossl@uci.edu

[1] Department of Logic and Philosophy of Science, University of California, 3151 Social Science Plaza A, Irvine 92697-5100, USA

Introduction

Modern medicine is often said to have originated with various scientific achievements in the late nineteenth century. At this time, germ theory gained favor in many scientific communities and overshadowed earlier theories of disease. Many of these earlier theories attributed diseases to long lists of sometimes ill-defined causal factors, while germ theory placed causal responsibility on identifiable, material contagions such as bacteria. In particular, the research of Koch and Pasteur led to the identification of single bacterial causes for diseases such as anthrax, tuberculosis, and cholera, which ranked among the leading causes of disease at the time. This research is often viewed as supporting a monocausal model in which single pathogenic factors are viewed as the main causes of particular diseases.

This nineteenth century germ theory model is often viewed as an important advance in medical theory that continues to have a lasting influence on modern medicine. The success of this theory is typically associated with its commitment to an underlying principle referred to as the "doctrine of specific etiology". This phrase was coined by René Dubos in reference to the theory's specificity at the level of disease causation or etiology (Dubos 1959, 102). This notion of specificity is typically interpreted in terms of a monocausal view in which particular diseases have single main causal factors. The perceived importance of this doctrine is difficult to overemphasize. The doctrine of specific etiology is viewed as "the most powerful single force in the development of medicine during the past century" (Dubos 1965, 326), "a singular turning point in the history of medical thought" (Loomis and Wing 1990, 1), "the theoretical core of modern medical ideology" (Lander 1978, 78–81), and the "signature of modern Western medicine" (Mishler 1981, 7). Additionally, this doctrine is considered "an assumption central to the medical practice" (Tesh 1988, 122), the "metanarrative" of modern medical theory (Downing 2011, 58), and a "prototype for explaining most diseases" (Aronowitz 1998, 8) that has "a lasting preeminence" in medicine today (Aronowitz 1998, 8).

There are a number of puzzles associated with the perceived importance of this doctrine. First, it is not always clear exactly what is meant by the doctrine of specific etiology. The literature lacks a clear account of the types of specificity present in this model and why exactly they matter. Second, while many scholars interpret this doctrine in terms of a monocausal picture, they also admit that most diseases have many causes and, thus, do not fit this view (Blaxter 2010). This is expressed in Dubos's quote from above and in the work of others who claim that the monocausal model has "serious limitations" due to its "oversimplification" of disease causality (Locker 2018, 19; Mishler 1981, 14). If the doctrine of specific etiology has these issues, then why is it viewed as a significant advance in medical theory that has led to the development of modern medicine? These puzzles raise further questions. First, what kinds of specificity are present in this early model of disease? Second, what makes them important and how have they influenced modern medicine, if they have at all?

This paper argues that the nineteenth century germ theory model involves two types of specificity at the level of etiology. One type receives significant attention

in the literature, but its influence on modern medicine has been misunderstood. A second type is present in this model, but it has been completely overlooked in the extant literature. My analysis discusses how these types of specificity led to a novel conception of etiology that continues to figure in medical theory today. This is an effort to clarify what has been viewed as "a profound change in ideas about disease causation that occurred in the late nineteenth century" (Kunitz 1987, 379). The rest of this paper is structured as follows. First, I provide some theoretical and historical background on conceptions of etiology with attention to eighteenth and nineteenth century medicine. After this, I discuss particular features of the germ theory model, including the types of specificity it contains. This analysis begins to indicate how these features have had a lasting influence on modern medicine, while a more detailed discussion of this is left for the end of the paper.

Two questions

Etiology is derived from the Greek work for cause ("aitia") and it refers to the causal factors that produce disease. As causes are always relative to their effects, identifying etiological factors or disease causes requires the specification of some disease trait of interest. This leads to an initial question of (1) how to identify and characterize distinct disease traits for the purposes of etiological understanding. Once this question is answered, and a disease trait is specified, a second question can be pursued. This second question involves (2) how to identify disease etiology or the factors that cause a given disease.

Consider the first (1) question, which involves how to identify and characterize disease traits for the purposes of etiological study. A general approach that has been involved in this process from Hippocractic to modern times involves the observation of various signs and symptoms that are viewed as characteristic of disease.[1] Individuals presenting with any one of a number of symptoms are often thought to be suffering from disease. These symptoms include manifestations such as chronic cough, diarrhea, fever, vomiting, lethargy, malaise, severe pain, and skin rashes, among many others. When these symptoms manifest in individuals they often present in particular groups or clusters that reoccur in different individuals with minor variations. This attention to symptomology encouraged a strategy of defining disease traits on the basis of particular symptom clusters. In the eighteenth and early nineteenth century, this symptom-based orientation commonly figured in conceptions of disease. For example, individuals who presented with a slow-onset of features such as bleeding gums, weakness, lethargy, and easy bruising were often diagnosed with a disease called scurvy. Another

[1] Technically, signs refer to features observed by a third-party (e.g. heavy breathing, pallor, and fast heart-rate), while symptoms refer to features experienced by a patient that cannot be observed in the same way (e.g. nausea, pain, and fatigue). As my analysis does not rely on this distinction, I follow the common practice of referring to both as "symptoms".

example is cholera, which was a disease attributed to individuals presenting with an acute onset of severe vomiting, diarrhea, sunken eyes, and labored breathing that often resulted in death. While these diseases were associated with a cluster of symptoms, the presence and severity of each symptom often varied from patient to patient.

Once a disease trait is specified, a second question can be pursued: (2) how to identify disease etiology or the factors that cause a given disease. In the eighteenth and early nineteenth century, most diseases were thought to involve long lists of causal factors. These causes were interpreted in the context of various disease theories, including humoral, miasmatic, contagion, and nervous system accounts. Humoral theories originated with ancient Greek medicine and involved the view that disease resulted from an imbalance of the four humors of the body (blood, phlegm, black bile, and yellow bile). Miasmatic theories maintained that "immaterial," noxious gases—referred to as "miasmas"—spontaneously emanated from rotting material and caused various epidemics. Contagion theories, on the other hand, attributed these epidemics to material contaminants that were physically transmitted from patient to patient. Finally, nervous system theories viewed disease as a byproduct of various dysfunctions of the nervous system.

The disease causes postulated by these theories were often divided into either predisposing or exciting factors, which had different types of causal influence over disease. Predisposing factors merely increased disease susceptibility, while exciting factors were triggers that provided a higher likelihood of disease occurrence. This predisposing and exciting framework supported a multicausal understanding of disease by expanding the scope of factors that were viewed as disease causes. In particular, this framework included religious, climate, astronomical, and moral considerations as causally relevant to disease. For example, religious considerations such as prayer and faith in God were included because a lack of either could predispose to disease by producing a stressed disposition (Tesh 1988, 17; Smith 2002, 922). A similar rationale expanded disease causes to include weather and environmental factors (such as dampness and cold), astronomical factors (including the location of the planets), and immoral factors (such as drug use and other "debauched habits" of the "lowest caste") (Harrison 2013, 15). There was often little consensus on which factors were predisposing or exciting causes and what combination of each was required to produce disease. Nevertheless, standard views maintained that many causal factors were operative in producing disease, where these factors were supported by different theories and capable of having different types of causal influence.

Consider how diseases like scurvy and cholera were explained within this multicausal framework. Scurvy was said to be caused by factors that included poor hygiene, putrefaction of the humors, indolence, drug use, moist air, bad water, a diet lacking in fresh vegetables, depression, and a lack of discipline (Harrison 2013). Similarly, cholera was attributed to a lack of exercise, excessive alcohol consumption, a lack of religious belief, noxious air, bacterial infection, mental exhaustion, and a lack of nourishing food (Smith 2002). This framework was characterized by multicausality in at least two ways. First, it maintained that a given instance of disease was produced by many causal factors and, second, that different instances of the same disease were produced by different combinations of these factors.

This multicausal framework involved a number of challenges. First, this framework made it difficult to provide concise characterizations of etiology because so many causal factors were viewed as relevant to disease. Second, it was often difficult to reach consensus on the relevant etiological factors because they could vary across instances of the same disease. In other words, there was no stable set of causal factors for a given disease category. Relatedly, even for a single case of disease it was not entirely clear how to identify which factors produced the disease and which did not. For any situation in which disease presented, one could always find more and more factors to include in its etiology without there being a clear basis for excluding any. This led to a very "flexible" disease model that could fit any situation because it "could accommodate virtually any pattern of observed data" (Smith 2002, 922). While this flexibility allowed the model to accommodate any situation, it prevented the model from being useful in various ways. For example, despite being able to "explain" disease after the fact, this framework could not provide information relevant to predicting or controlling disease before it occurred. The long lists of causal factors identified within this multicausal framework led to an equally long list of factors that could be targeted to potentially cure, treat, and prevent disease outcomes. This framework led to therapies such as avoiding cold and damp climates, bloodletting to restore the balance of the humors, prayer meetings and religious fasts, forced blistering of the skin to correct overstimulation of the nerves (vessiculation), eating fresh fruits and vegetables, avoiding alcohol, keeping flowers and burning tar and pitch to purify the air of miasmas, and avoiding dirty water due to potential contagions (Tesh 1988, 18; Smith 2002, 922). While some of these therapies had limited success, most of them failed to provide any control over disease outcomes (and some even exacerbated disease).

Things began to change considerably around the mid-to-late nineteenth century. At this time advances in experimental methods, laboratory techniques, and views on bacterial species encouraged further examination of contagionist accounts of disease. It was discovered that livestock who fell ill with anthrax—a disease associated with fever, swelling, difficulty breathing and eventually death—often had large rod-shaped particles in their blood, which were thought to be bacteria. It was not clear if these particles were causative, associative, or mere by-products of the disease. In a landmark set of experiments, Robert Koch demonstrated that these particles were a single species of bacteria and that when pure cultures of these bacteria (or their spores) were inoculated into animal models, they reliably contracted the disease (Koch 1876). In particular, this research showed that the disease *always* occurred after the introduction of a specific bacterial species and that it *never* occurred without it. Koch claimed that this step-wise procedure, referred to today as "Koch's postulates," was "proof" that this bacteria was the cause of anthrax. In little time, most contemporary researchers agreed with him. Similar experiments were performed with tuberculosis, diphtheria, and cholera, and in each of these cases, distinct bacterial species were identified as the causes of these diseases.[2] This led to a "germ

[2] Experiments with cholera differed from other diseases in the sense that Koch could not identify animal models susceptible to the cholera bacilli. In this case, he relied on "natural experiments" to complete the proof that this bacilli caused this disease (Ross and Woodward 2016, 40).

theory" model where single bacterial contagions were viewed as the main causes of particular diseases.

This nineteenth century germ theory model began gaining favorable attention and it would eventually overshadow earlier multicausal theories of disease. Modern analyses claim that this model is guided by the "doctrine of specific etiology" in which diseases are caused by "specific" bacterial factors. These analyses typically emphasize how quickly this model was accepted by the contemporary research community. As Dubos states, "[t]here is no more spectacular phenomenon in the history of medicine than the rapidity with which the germ theory of disease became accepted by the medical profession" (Dubos 1965, 324). Why was this theory so quickly accepted? What types of specificity are present in germ theory and why are they important, if they are at all? I address these questions by relying on an expectation that has been present in medical reasoning from the eighteenth century to modern times—the expectation that disease causes have control over disease outcomes.

The "germ theory" of disease: an etiological framework

The expectation that causes control their effects is found in many contexts of causal reasoning, including medical contexts from the eighteenth century to modern times. One notable feature of the nineteenth century germ theory model is that it identified factors as disease causes when they provided causal control over disease outcomes. The relevant notion of "causal control" that I have in mind is helpfully clarified by Woodward's (2003) interventionist account of causation and it can be understood in the following manner:

(I) X has causal control over Y if and only if an intervention that changes the value of X (and no other variable) in background circumstances B results in a change in the value of Y.

This account relies on the notion of an ideal intervention. An ideal intervention involves an unconfounded manipulation of X with respect to Y where the changes in Y are produced by changes in X and not through any other variable. In other words, this intervention on X: (1) is not correlated with another variable W that causes Y, (2) it does not directly cause Y, and (3) it does not influence any of the causal intermediates between X and Y (Woodward 2003). This ensures that when X is manipulated and changes in Y are identified, the changes in Y are caused by X and not some other factor. It is important to note that the notion of an ideal intervention is not restricted to those interventions that we can actually perform. This captures the fact that we often make causal claims about factors that we cannot actually manipulate.[3] In these cases we often consider hypothetical interventions in the sense that if

[3] For example, we make causal claims about past events which we cannot intervene on (yesterday the rain caused flooding) or current events which are beyond our technological capacity for actual intervention (such as, the location of the moon causing changes in the tides).

a candidate cause were manipulated, some effect variable would change.[4] In applying this framework to a simple case of disease causation, we can think of X as a candidate cause and Y as a disease trait where each variable can take on the values (0,1), representing the absence and presence of each entity. If X is a cause of Y, it should be the case that intervening on X to change its value produces changes in the value of Y.[5]

This account helps clarify why earlier multicausal theories of disease were so unsatisfying. The causal factors identified by these theories were expected to have control over disease outcomes, but they often failed to meet this standard. Furthermore, some of these causes were defined in ways that evaded scientific examination and consideration. For example, disease-causing miasmas were sometimes understood to be "non-physical" gases (Kinzelbach 2006, 388), and in this sense, there was no conceivable intervention that could possibly manipulate such an immaterial cause.[6] The same could be said for religious considerations such as evil spirits and disease-causing demons. With no way to even conceive of (much less carry out) physical interventions on these "supernatural" factors, the question of whether they played a causal role in disease could not be experimentally tested or even rendered into a sound scientific framework.

Additionally, the reasoning behind the germ theory model and its quick acceptance by this scientific community are well-explained by the interventionist account. The experiments used to support this model represent a paradigmatic interventionist experiment. They involve intervening on a candidate cause (a type of bacteria) with respect to an effect of interest (a particular disease). As manipulating the presence and absence of the bacteria controls whether the disease manifests or not, the bacteria is viewed as a cause of this disease. This experimental evidence refuted common claims that bacteria were simply harmless contaminants or uninteresting byproducts of the disease process. Furthermore, it makes sense that factors with interventionist control would be of interest to medical researchers given the goals of this scientific community. Factors that control disease outcomes can be targeted to create successful treatments and preventions, and they can explain why particular communities have disease outbreaks while others do not.

This interventionist analysis differs from common interpretations of germ theory, which view causal claims as well understood in terms of claims about necessary and sufficient conditions (Carter 1985, 2003; Smith 2007; Broadbent 2009).[7] In recent

[4] This involves a counterfactual claim (if X were to be changed, then Y would be produced), which is why this is often called a counterfactual account of causation. In the rest of this paper, when I discuss interventionist control I mean hypothetical causal control in this sense.

[5] Whether this type of causal claim is supported by experimental work or not depends on how the relevant intervention and causal variables are defined (Hernán and Taubman 2008; Woodward 2016).

[6] Not all conceptions of "miasma" had this feature—others were associated with material substances and even physical contagions, both of which could be targeted with interventions aimed at cleaning and purification. In fact, some notions of "miasma" overlapped with the concept of physical "contagion" (Kinzelbach 2006).

[7] A standard example of such a necessary and sufficient condition account is Mackie's INUS condition framework (Mackie 1965) and similar accounts are found in the natural sciences (Rothman 1976; Rothman and Greenland 2005).

work, it has been argued that there are a number of problems with the necessary and sufficient condition interpretation and numerous advantages to an interventionist one (Ross and Woodward 2016). With respect to Koch's work, necessary and sufficient condition interpretations do not accommodate his emphasis on experimental procedure and his interest in ruling out confounders, which are both key features of an interventionist framework. Furthermore, there are normative issues with the idea that "cause" can be defined in terms of necessary and sufficient conditions—notably, that these views fail to distinguish causation from correlation.[8] Of course, the fact that this conception of causation is problematic does not mean that Koch failed to hold such a view. However, given his interest in ruling out confounding and the central role of interventionist experiments in his causal "proof," it would be unexpected for him to hold a view of causation that does not fit with these features and that fails to distinguish causation and correlation. As Ross and Woodward (2016) claim, the causal criteria found in Koch's work "make sense and are normatively justified within an interventionist framework and are more difficult to understand within alternative frameworks for thinking about causation" (Ross and Woodward 2016, 40).[9]

Single-cause specificity: monocausal etiology

In addition to meeting the interventionist criterion (I), causes identified by the germ theory model also have particular types of specificity at the level of etiology. One type of specificity that is present in this model is what I call single-cause specificity. This can be characterized as follows:

Single-cause specificity (S_1): for a given instance of disease D a single factor C causes D in the sense of (I).

This type of specificity maintains that a single factor C has interventionist control over an instance of disease D, where the contrastive focus of D is the presence (1) and absence (0) of the disease. This contrasts with a situation where multiple factors

[8] For other problems associated with these "regularity" accounts of causation, see (Hitchcock 2018).

[9] This interventionist interpretation should not be viewed as "anachronistic" as one reviewer suggests. It is entirely possible (and I think, likely) that Koch and others expected causes to provide interventionist control over their effects—and that they developed methods and experiments based on this rationale—even if they were unfamiliar with anything similar to modern interventionist accounts of causation. Relying on a causal criterion that is guided by an interventionist rationale (or any other) does not require articulating exactly what that rationale is. The same point holds for scientists in modern contexts—we often find that their causal criteria are well-interpreted with particular philosophical accounts of causation, even when they are completely unfamiliar with such accounts. In some sense, this should be unsurprising. Scientists are often more interested in establishing causal criteria, showing how they work, and what their merits are, as opposed to clarifying their underlying rationale in terms of philosophical, theoretical, or logical concepts. Relatedly, interventionism aims to capture and clarify the reasoning that is already present in successful scientific work on causation. The interventionist account can be understood as making explicit the connection between causation and control that is already present in this work.

interact together to provide this type of control over D. To be clear, this type of specificity (S_1) does not deny the possibility of dividing up the causal process between C and D into a sequence of multiple causal intermediates.[10] What it does deny is that there are other factors—off this path—that also have interventionist control over the disease. What about factors such as oxygen, the immune system, and genes? Do these factors play a causal role in all diseases and, thus, figure in the multicausal etiology of any disease? Notice that we do not typically cite these factors as causing infectious diseases such as tuberculosis, anthrax, and cholera. The reason for this is that we do not know of any immune or genetic factors that would provide causal control over these infectious diseases when hypothetically manipulated. When these factors are manipulated, they can control a variety of outcomes (including whether an organism lives or dies in the case of oxygen), but they lack control over the effect of interest, namely the presence and absence of the disease in question (Meehl 1977, 38). There is a sense in which these immune and genetic factors are necessary background conditions for bacterial contagions to exert the causal control that they have, but such immune and genetic factors lack this type of control themselves.[11] This reasoning does not deny that immune and genetic factors cause some diseases—in fact, they meet the single-cause specificity (S_1) standard for diseases like pemphigus and cystic fibrosis, respectively.

Diseases that meet this type of specificity (S_1) have a *monocausal etiology* in the sense that they can be controlled by single causal factors. Most interpretations of germ theory and the doctrine of specific etiology involve this "monocausal" or single cause view. Additionally, these interpretations often claim that germ theory expected all diseases to meet this monocausal standard. For example, germ theory is said to involve the view that "that every disease has a single specific cause" (Cockerham and Richey 1997, 35) and that "[i]f you find that cause, you can control the disease" (Agar 1994, 394).[12] While nineteenth century researchers certainly viewed this monocausal standard as applying to the infectious diseases they studied, it is not clear that they viewed it as a universal standard that all diseases should meet. Nevertheless, as I suggest below, there are features of this germ theory framework that do apply to diseases more generally.

If we look to modern medicine we find that many diseases meet this type of specificity (S_1). These examples do not just include the infectious diseases that this model

[10] In fact, disease etiology is sometimes depicted as a linear process where upstream causes represent the "etiological" factors and the causal intermediates represent the "pathological" process. However, these terms are sometimes used synonymously and often without much clarity (Wullf and Gotzsche 2000, 55).

[11] What about alternative interventions that also prevent disease such as (1) preventing cattle from grazing in a field contaminated with anthrax spores or (2) vaccinating the cattle with an attenuated form of the bacterium? Do these alternative interventions strain this claim of "monocausality" by identifying alternative causes? Neither of these should be viewed as inconsistent with single-cause specificity, because they both involve targeting the same single causal factor. The reason why preventing cattle from grazing and vaccinating them work is because they target the single bacterial factor responsible for the disease (or the spore that produce this bacterium). In other words, just because different interventions can target the same causal factor does not mean there are multiple causes.

[12] Other statements of this monocausal interpretation can be found in: Locker (2018, 19), Stewart (1968, 1077), Aronowitz (1998, 196), Stephenson (1985, 355), and Dubos (1959, 102).

began with but also nutritional, genetic, viral, immunologic, and parasitic diseases.[13] This reveals a lasting presence of the monocausal framework in modern medicine and its extension to a wider range of cases than those it was originally applied to. However, while some diseases fit this model others clearly do not. Some diseases are produced by multiple interacting factors that share control over disease occurrence. Consider the case of phenylketouria (PKU), which is a neurologic disorder involving severe brain damage. The occurrence of this disease is controlled by both a gene variant and a dietary factor. Both of these factors meet the interventionist criterion (I), but their causal control is dependent on each other, which is to say that they are "interacting causes" (Spirtes et al. 2000, 40). The gene variant only provides control when the dietary factor is present and the dietary factor only provides control when the gene is present. Gaining control over this disease requires manipulating both factors. PKU does not fit the monocausal framework because instances of this disease are controlled by multiple, as opposed to single, causal factors.

If the notion of monocausal etiology does not apply to diseases more generally this might suggest that the germ theory model is quite limited in application and that it lacks significant bearing on modern medicine. This is a common view in the literature.[14] This position overlooks an important principle that originates with germ theory and that applies more broadly to disease causation—the goal of identifying factors that provide control over disease outcomes, however many factors are required to meet this goal. In contrast with the notion of monocausal etiology, this principle involves the notion of *causal etiology*—this refers to the selection of disease causes on the basis of their control over disease outcomes without specifying the number of causes involved. This perspective maintains that the success of germ theory did not just lie in the identification of single causes but in identifying causes with control over disease. This is a key feature that distinguishes this theory from earlier multicausal views. Of course, for the diseases to which germ theory was originally applied, single factors just so happened to provide this control. However, for other diseases such as PKU, the same principle applies and functions to guide the identification of multiple causes. This notion of causal etiology has wide applicability in medicine and it remains a feature of our modern conception of disease etiology.

Before moving on, it will help to relate this analysis to a common criticism of the germ theory model. The germ theory model—and its monocausal character—receive heavy criticism in the philosophical, historical, and medical literature, on the

[13] For example, consider (a) scurvy, (b) Huntington's disease, (c) chicken pox, (d) pemphigus, and (e) giardiasis, respectively. These are all diseases that are viewed as having single causal factors. These causes include: (a) a deficiency of vitamin C, (b) a mutation in the *huntingtin* gene, (c) the varicella virus, (d) antibodies toward an anchoring protein in the skin (desmosomes), and (e) the parasite *Giardia lamblia*, respectively.

[14] For examples of this view, see: Blaxter (1990, 4), Broadbent (2009, 305; 2013, 161), Stewart (1968), and Rothstein (2003, 223).

grounds that most (if not all) diseases have multicausal as opposed to monocausal etiologies.[15]

These criticisms are often coupled with a distinct story about the development of modern medicine. In particular, it is frequently suggested that in modern medicine we now have an accurate, sophisticated, and well-informed *multicausal* view of disease, which is a response to the "oversimplified," immature, and "inchoate" *monocausal* framework of germ theory (Loomis and Wing 1990, 2; Broadbent 2013, 161). This characterization is often used to rationalize the development of our modern multicausal understanding of disease and give it a clear contrast with the "naiveties" of earlier disease theories (Broadbent 2013, 302). However, this characterization appears narrow-sighted when one appreciates the history and motivation that led up to the nineteenth century germ theory of disease. This is because we had a multicausal theory of disease well before nineteenth century germ theory was ever established, but it did not work very well. In fact, as argued above, in many ways germ theory was a response to an overly flexible multicausal framework and part of its success involved stricter requirements of what counted as a disease cause—at the very least, requiring that these factors control disease outcomes. The fact that we still see this requirement in modern disease theories—whether single or multiple causal factors are involved—reveals the lasting influence of this view. Germ theory is largely responsible for this shift from a more flexible conception of disease etiology to one that maintains that disease causes should provide control over disease outcomes. A key to appreciating the influence of germ theory on modern medicine requires identifying its focus on labeling factors as causes when they provide control over disease outcomes—a feature that earlier multicausal theories lacked. This principle is inherent to the selection of single and multiple factors as disease causes in modern medicine, but the origination of this principle with germ theory has not been sufficiently acknowledged in the literature.

Shared-cause specificity: shared etiology

The nineteenth century germ theory model involves a second type of specificity that has received little to no attention in the philosophical literature. I refer to this as shared-cause specificity and it can be characterized as follows:

[15] Consider a related objection to the single-cause specificity standard: in some cases, an individual can harbor the bacterial contagion without acquiring the disease. This is seen in cases of "healthy carriers" and it has been used to deny the validity of a single-cause type view (Stewart 1968). For example, although rats injected with anthrax bacteria invariably acquired the disease, the fact that cattle could remain disease-free after being fed anthrax spores, was used to question this causal link. What this objection often fails to keep in mind is that to say that bacteria have causal control over disease does not imply that they have this control when present in any body location. Disease susceptibility depends on the contagion being in particular (but not just any) bodily locations. Thus, finding locations where bacteria can reside without producing disease does not disprove the causal establishment, so long as there are locations where they do produce disease (and thus, exhibit causal control).

Shared-cause specificity (S_2): for all instances of disease D the same factor C or the same combination of factors ($C_1, C_2, \ldots Cn$) cause every instance of D in the sense of (I).

This type of specificity ensures that a population-wide disease trait has a homogeneous etiology in the sense that every case of the disease is produced by the same causal factors. Notice that the infectious diseases originally studied with the germ theory model meet this standard. For example, all cases of anthrax are caused by the anthrax bacterium. Shared-cause specificity does not pertain to the number of factors that cause an instance of disease—it has to do with whether these factors are the same or different across all instances of the disease in question. Thus, diseases do not need to meet the monocausal model in order to satisfy S_2.[16] This is seen in the case of PKU, which satisfies S_2 because every case of this disease is caused by the same two factors. Shared-cause specificity contrasts with a situation where distinct instances of the same disease outcome are caused by different, heterogeneous factors. This situation of heterogeneous etiology was common in eighteenth and early nineteenth century explanations of disease. At this time, for example, it was thought that different cases of cholera were caused by completely different combinations of causal factors. Germ theory, on the other hand, conflicted with this heterogeneity and involved shared-cause specificity because it viewed this disease as having a shared etiology where all cases of the disease were caused by a particular bacterium (the comma bacilli).

Diseases that meet this type of specificity (S_2) have a *shared etiology* in the sense that the causes across all instances of the disease are shared. Why should this be viewed as a type of specificity? Both S_1 and S_2 are forms of causal specificity in the sense that they identify something singular about a causal process given an effect of interest. S_1 refers to a single-cause for a particular instance of disease, while S_2 refers to a single set of causes for all instances of a given disease. Identifying a shared etiology for some disease trait has a number of advantages over situations of etiologic heterogeneity. As shared etiology identifies causal factors that are common across cases of a particular disease, these factors can be targeted to explain and potentially control most or all of the cases of the disease in the entire population. Alternatively, if a disease fails to meet S_2 and has a heterogeneous etiology, these advantages are

[16] In other words, single-cause specificity and shared-cause specificity are not mutually exclusive. Suppose each case of anthrax has a single cause but that there are different single causes across cases (e.g. five different bacteria are individually sufficient to produce this disease). This is a situation that meets S_1 but not S_2. Alternatively, consider a situation where every single case of anthrax is produced by multiple causes, but these causes are the same across all cases of the disease. This is a situation that meets S_2 but not S_1. Our accepted explanation of anthrax meets both of these standards—we view the disease as caused by a single bacterial species (S_1), where every disease instance has the same cause (S_2). A situation that meets neither standard would involve there being multiple causes for each instance of disease (lack of S_1) where these causes differed across cases (lack of S_2). Multicausal theories of disease in the eighteenth and nineteenth century often fall into this final category and meet neither type of specificity. This highlights how distinct germ theory is from these earlier views, as it contains both types of specificity (S_1 and S_2).

lost. In this situation, any single factor or combination of factors will only pertain to a subset of all of instances of a given disease, as opposed to most or all of them.

In modern medicine, the notion of shared etiology is often referred to as a "causal signature" (Murphy 2006, 105), "disorder-specific pathophysiology" (Caspi and Moffitt 2006, 586) "shared causal process" (Zachar 2014, 87), "shared pathogenesis" and "unifying cause" or "unifying theoretical underpinning" for a given disease (Egger 2012, 1). In the context of our current medical theories, there is a common default assumption that diseases—insofar as they are understood or classified etiologically—should have shared etiologies in the sense of S_2. Shared etiology is often used to justify divisions between disease categories on the grounds that distinct etiologies represent distinct diseases.[17] In order to see this, consider the example of Parkinson's disease. Fairly recently, researchers discovered that distinct cases of Parkinson's disease are caused by completely different causal factors (i.e. that it has a heterogeneous etiology).[18] When researchers discovered this, they viewed it as a significant problem for explaining and understanding this disease, and they suggested dividing up this disorder on the basis of these factors. In fact, they claimed that "it would be helpful to replace 'Parkinson's disease' with a term that is not saddled with implications of a single causal mechanism" (Calne 1989, 18). Notice that referring to a condition as a disease implies that it is produced by a "single causal mechanism" where this does not refer to a single causal factor, but rather a single set of causes that are common across instances of the same disease. Referring to each of these cases as "Parkinson's disease" was viewed as problematic because they lacked a shared etiology which disease traits are often expected to have. This expectation is captured by Meehl who states that "[i]t is counterintuitive to speak of two 'specific' etiologies for the same disease" (Meehl 1977, 44). Thus, when a disease trait is identified as having a heterogeneous etiology, it is often suggested to divide-up the trait on the basis of these heterogeneous factors because this would allow it to conform to the shared etiology standard. A second solution is to continue searching for some shared etiology that unifies the heterogeneous causes. This can be done by identifying a "final common pathway" that the heterogeneous causes converge on and operate through in producing the disease outcome (Weber 1999).

Shared etiology is also used to justify the identification of "valid" or "legitimate" disease traits and categories.[19] In fact, when medical researchers use the term "validity" they often explicitly rely on the notion of shared etiology.[20] Consider the case of psychiatric disorders—these disorders are based on shared symptoms but often lack

[17] As Calne states, "[a]etiology is a fundamental criterion for the delineation of individual diseases" (Calne 1989, 18).

[18] Parkinson's disease can be caused by (1) single gene variants, (2) single environmental factors (such as the drug MPTP, pesticides, and even viral encephalitis), and (3) combinations of genetic and environmental factors (Nandipati and Litvan 2016).

[19] For an overview of the uses, meanings, and applications of the term "validity" in this context, see Schaffner (2012).

[20] As Hyman states, "I use the term 'diagnostic validity' throughout this review…as shorthand to signify definitions that capture families of closely related disorders with similar pathophysiology" (Hyman 2010, 162).

known or identifiable etiologies. In these cases, there is a common worry that these categories might group together patients with similar symptomology but different etiologies. If this were the case, these categories would be subject to modification and would be redrawn in accordance with the shared etiology standard. However, as the causes of these disorders remain "stubbornly out of reach," whether they are valid or not remains an unanswered question until their causes are better understood.[21] This leads researchers to view these categories as characterized by "instability" (Kendler and Zachar 2008, 370) and as "provisional" (Kendell and Jablensky 2003, 4). These categories represent disease traits that are "open concept[s]" (Meehl 1977, 34) and have yet to be sufficiently verified and accepted by the medical community.

Skepticism about these disease categories does not just involve worries about heterogeneous etiology, but also worries about the lack of any etiological understanding of these disorders. Although common symptom profiles are used as a first-pass method for discovering diseases, these traits are not considered valid or legitimate until their etiologies are identified. The relevant notion of etiology here is derived from germ theory and refers to factors that meet the causal etiology and shared etiology standards. Part of what this reveals is that germ theory has not just influenced our modern conception of etiology, but also how we conceive of and classify disease traits. This is because we expect valid disease traits to meet these etiological standards. This is expressed by Hull when he claims that "[i]n efforts to understand, control, and avoid disease, modern medicine has incorporated into the very identification of disease the notion of the cause of the syndrome. This permits the individuation of similar syndromes with distinct causes into different diseases" (Hull 1979, 61). Relatedly, for psychiatric conditions, the lack of some identifiable causal etiology leaves many to question whether a "valid" disease has been identified. This is expressed by the dominant view in medicine that "if you cannot explain a distinct and unambiguous etiology for a syndrome, preferably in biological terms, then you do not have a real disorder" (Kendler 2012, 1). This view does not deny that individuals "really" suffer from and experience psychiatric disease. Instead, it denies that our conception and categorization of these diseases will remain stable and fixed as we learn more about their etiologies. In other words, "real" disorders are stable disorders, and stable disorders have identifiable shared causal etiologies. This is why psychiatry is often referred to as a premature, "embryonic," or "nascent" science that is in its "early stages" and in a continuous "state of flux" (Hyman 2010, 151, 171; 2002, 140; Kendell and Jablensky 2003, 4; Jablensky 2005, 202). It has yet to

[21] One method used in attempts to uncover the etiologies of psychiatric disorders—and subsequently change their characterization and classification—are genome-wide association studies (GWAS). Researchers claim that "carefully designed GWAS with thorough phenotypic characterization have the potential to redefine disease classification" on the basis of identifying "distinct underlying pathological mechanisms" (Detels et al. 2015, 565). It is further claimed that for "complex diseases that have previously been regarded as distinct clinical entities, GWAS findings may point to common underlying disease processes and a shared pathogenesis" (Detels et al. 2015, 565). The assumption that diseases should meet the shared etiology standard (and notion of shared-cause specificity) is seen in these quotes.

uncover the etiologies of psychiatric disorders, which is viewed as a requirement for valid disease traits in modern medicine.

One response to this is that there are surely some diseases that do not meet the shared etiology standard. What about conditions such as cancer, high blood pressure, and headache? Do these represent cases where the same disease can be caused by different factors? Shared causal etiology is a standard applied to etiological conceptions and classifications of disease, but there are other ways to conceive of and classify diseases that need not meet this standard. For example, we sometimes classify disease traits on the basis of anatomic location, physiological subsystem, widespread malfunction, or form of trauma because these are useful in various contexts.[22] Additionally, various signs, symptoms, and injuries are often referred to as diseases, despite failing to meet the shared etiology standard. So first, the claim that diseases are often expected to meet shared etiology does not deny that some helpful categorizations do not abide by this. This is because not all categorizations are guided by etiology. Second, researchers often distinguish conditions that are colloquially referred to as diseases from traditional, etiological conceptions of disease. In other words, many of these counterexample categories are not viewed as properly representing *individual* or *single* disease traits. Instead, they often group together multiple conditions where each condition is viewed as a distinct disease (as in the case of cancer), or they pick out particular features that are viewed as one of many symptoms associated with a single disease (as in the case of headache). The distinction between these purported counterexample cases and a traditional, etiological conception of disease has motivated researchers to suggest limiting the use of the term "disease". As Stehbens states:

> "The word disease must be restricted in usage to indicate a specific malady and not used carelessly or synonymously with (1) symptoms, signs, or laboratory findings, e.g., headache, hypertension, pyrexia, hypercholesterolemia; (2) nonspecific complications, e.g., embolism, hemorrhage, ischemia, necrosis; and (3) a group or class of pathological states, e.g., stroke, subarachnoid hemorrhage, myocardial ischemia, CHD. Each is a manifestation of several diseases and not a final diagnosis in itself, even though often regarded as such clinically" (Stehbens 1992, 98).

This passage suggests that there is resistance in the medical community toward viewing these purported counterexample cases as legitimate single disease categories. Furthermore, even if these cases are viewed as legitimate disease examples, I am content with restricting my analysis to the influence of germ theory on the traditional, etiological conception of disease.

[22] As Calne states, "[d]iseases have been been grouped wherever there are any common features that facilitate discussing them for the purposes of teaching, diagnosis, treatment, or research. But the factors that provide cohesion for each of these disciplines are totally different, so it is not surprising that the classification is so heterogeneous" (Calne 1989, 19).

Further comments: specificity of clinical presentation

This analysis has considered two forms of specificity in the germ theory model: single-cause and shared-cause specificity. These types of specificity are present at the level of disease causation or etiology. Consider another form of specificity that has to do with disease effects or outcomes: specificity of clinical presentation. Specificity of clinical presentation can be taken as referring to a specific set of symptoms that reliably occur in cases of a given disease. Despite common claims,[23] this type of specificity is not present in the germ theory model. Diseases that meet the etiological standards outlined by germ theory lack specific clinical presentations in this sense. For these diseases, symptomology can differ across cases of the same disease and it can be similar across cases of different diseases. This is also true of modern disease traits that meet these etiological standards.[24] In other words, shared causal etiology does not reliably track specific, repeatable symptom patterns and, relatedly, symptom patterns alone do not reliably distinguish etiologically distinct disease traits. This clarifies two ways in which information regarding symptomology (or clinical presentation) is limited in particular kinds of medical decision-making. The variability of symptoms with respect to etiologically defined diseases means that more than just symptomology is often needed to diagnose a patient with a particular disease.[25] This makes sense of how difficult diagnosis is in modern medicine, where—if diseases did have specific clinical presentations—one would think that diagnosis would be much easier. The fact that unique symptom clusters fail to reliably track particular etiologies also makes sense of the fact that "symptom-based" diseases are viewed as "tentative" categories that are subjected to significant scrutiny. This is because symptomology alone does not provide a guarantee of shared, causal etiology, which is the gold standard for valid and legitimate disease traits.

Influence on modern medicine

I have outlined three key features of the nineteenth century germ theory of disease. Within this framework, disease causes meet the interventionist criterion, single-cause specificity, and shared-cause specificity. Single-cause specificity and shared-cause specificity correspond to the notions of monocausal etiology and shared etiology, respectively. Furthermore, I have suggested that monocausal etiology is importantly related to the notion of causal etiology. Both refer to factors with control

[23] For these claims see Rothstein (2003, 222) and Blaxter (1990, 4).

[24] For example, two patients with tuberculosis can present with completely different symptoms, while a patient with tuberculosis and a patient with asthma can present with similar symptoms.

[25] Pathognomonic signs are an exception to this claim as they are signs that are unique to particular diseases. An example of these signs are koplik spots, which are oral lesions found in cases of measles and no other disease. As pathognomic signs are unique to particular diseases, their identification often allows for an immediate and reliable diagnosis without needing to seek further information. These signs are highly useful for diagnostic purposes, but they are also extremely uncommon. Most diseases do not have pathognomic signs.

over disease instances, but the monocausal case maintains that one factor provides this control, whereas the causal case does not specify how many factors provide it. This leaves us with three important features of germ theory: it identifies factors as disease causes when they meet (a) the interventionist criterion, (b) causal etiology, and (c) shared etiology. These standards for disease causation are far more stringent than those present in earlier multicausal theories of disease, and they help capture how etiology is understood within the germ theory model. I refer to these three features as the "shared causal" etiology standard or characterization of etiology.

How has germ theory influenced modern medicine, if it has at all? In modern medicine, the notion of etiology is inherent to how diseases are understood and studied. This orientation is referred to as the "hard medical model" by Kendler and the "medical model" or the "biomedical model" by Engel and others (Kendler 2012, 1; Engel 1977, 39; Mishler 1981, 1–3). A core feature of this model is the view that disease traits and categories are legitimate to the extent that their causal etiologies are well-understood. What is meant by etiology is something similar to the shared causal etiology conception, which originated with germ theory. In fact, when scientists discuss the hard medical model, they often refer back to germ theory and the diseases to which it was originally applied.[26] However, the influence of germ theory is not just seen in our modern understanding of etiology. As etiology plays a central role in how diseases are classified, defined, and discovered, the influence of germ theory can be seen in all of these projects.

First, our modern conception of etiology has been significantly influenced by the etiological framework that originated with germ theory. While eighteenth and early nineteenth century theories were very permissive in what was viewed as causally relevant to disease, germ theory established a more rigorous set of standards that are similar to those present in medicine today. These standards are captured by the notion of shared causal etiology—the expectation that disease causes provide control over disease outcomes where these factors are shared across cases of the same disease. Modern medicine has adopted this restricted view of etiology and disease causation in the sense that not just any factors can be viewed as disease causes. When candidate factors lack causal control over disease traits or cannot conceivably or hypothetically be manipulated, their role in disease causation is denied. When heterogeneous causes are identified for a given disease, efforts are made to divide up the disease category or find other shared (or unifying) causes so that the shared etiology standard is met. Finally, when there are absolutely no identifiable factors that meet these standards, medical researchers admit that they have a disease of "unknown etiology," which is viewed as a tentative disease trait until suitable causes are identified. These standards explain the selectiveness of the medical community in identifying etiological factors, but also how they reach consensus on exactly which factors these are. This etiological framework provides an answer to the second question mentioned in the beginning of this paper, which is (2) how to identify disease etiology or the factors that cause a given disease. Once a disease trait is

[26] For examples of this, see: Kendler (2012, 2), Ahmed and Kolker (1979, 115), and Suls and Wallston (2003, xi).

identified, disease etiology is comprised of those factors that meet the shared causal etiology standard. The germ theory model provided a novel answer to this question and this answer is similar to the one we continue to give today.

Second, by influencing our modern understanding of etiology, germ theory has also shaped how we classify disease traits because we often expect proper disease categories to track shared causal etiologies. This explains why scholars claim that germ theory "placed disease classification on a radical new footing" (Aronowitz 1998, 13) and that it "led to the redefinition and reclassification of many disease entities by the criterion of cause" (Susser 1973, 23). In many ways, germ theory was the origination of our modern use of and preference for cause-based classifications of disease, in contrast with those that are symptom-based. Cause-based classifications are valued in medicine, in part, because they identify factors that can potentially allow for treatments, preventions, and cures. Alternatively, symptom-based classifications can usually only suggest therapies that provide symptom-relief without targeting the root cause of disease. Symptom-based classification is still present in modern-medicine for diseases that have poorly understood etiologies. In these cases, the categories are viewed as temporary placeholders until etiology is better understood. The sense in which etiology is the accepted guideline for disease classification, despite the need for temporary reliance on a symptom-based approach, is discussed by Hyman:

> In disease classification, the gold standard is either etiology or etiology modified by pathophysiology…For mental disorders, etiologic and pathophysiologic information is still sparse and thus cannot yet yield valid disease definitions. The result is a classification based, of necessity, on phenomenology (Hyman 2010, 161).

This symptom-based classification is sometimes referred to as involving "phenomenology" in the sense of merely describing the surface phenomena of these disorders without making reference to their causes. While disease classification in mainstream medicine is viewed as "theoretical," the classification of psychiatric disorders is referred to as "atheoretical" (Kendler 2012, 1), "descriptive" (Pritchard 2015, 8), and as relying on the "surface characteristics" of disease (Hyman 2010, 161). As suggested by Hyman's quote, etiology is often viewed as the theoretical backbone of modern disease classification. Relatedly, germ theory has also influenced how we conceive of and define legitimate disease traits because we expect these traits to have shared causal etiologies. This is seen in the context of psychiatry where disorders lacking this type of etiology are not viewed as "real" or legitimate diseases. Hyman mentions this in the quote above, in claiming that etiology guides "valid disease definitions". Part of what is so impressive about this is that it reveals how an understanding of etiology—or disease causes—has actually influenced how we think disease effects or disease traits should be properly understood. This is because we view valid and legitimate disease traits as those traits that meet the shared causal etiology standard. In other words, the notion of etiology that originated with germ theory has influenced how we define disease traits and how we think they are best understood. Thus, while the etiological framework of germ theory provided an explicit answer to question (2) it also implicitly answers question (1), which is how to identify and

characterize distinct disease traits for the purposes of etiological understanding. This is because current medical theory maintains that the ideal way to identify and characterize distinct disease traits is on the basis of shared causal etiologies. Until disease traits meet this standard, they are viewed as tentative conceptions that require further study to be accepted.

A third and final main influence of germ theory relates to the process of disease discovery. Germ theory captures a process of disease discovery that is still present in modern medicine. This process involves two main steps; first (4.1) specifying a shared cluster or pattern of symptoms and second (4.2) identifying the shared causal etiology for that cluster. This process is discussed by Kety and Engel:

> "The medical model of an illness is a process that moves from the recognition and palliation of symptoms to the characterization of a specific disease in which the etiology and pathogenesis are known and treatment is rational and specific. That progress depends upon the acquisition of knowledge and may often take many years or centuries. Numerous medical disorders and one or two mental illnesses have moved to the final stages of understanding, but many are still at various points along the way." (Kety 1974, 959)

> "Thus taxonomy progresses from symptoms, to clusters of symptoms, to syndromes, and finally to diseases with specific pathogenesis and pathology. This sequence accurately describes the successful application of the scientific method to the elucidation and classification into discrete entities of disease in its generic sense. The merit of such an approach needs no argument." (Engel 1977, 42)

In the first step of this process, repeatable symptom clusters are identified and used as potential guides in identifying etiologically distinct disease traits.[27] This first step represents an "early stage of knowledge" (Meehl 1977) in which diseases are identified on the basis of "descriptive" (Pritchard 2015, 8), "surface characteristics," which are not viewed as an accurate "mirror of nature" (Hyman 2010, 161, 158). This stage captures the "soft medical model" (Kendler 2012, 1), in which diseases are merely "open concepts" (Meehl 1977, 34) that are defined and classified within a symptom-based framework. A main goal in disease discovery is to get to the second stage where shared, causal etiologies are discovered for these traits. Most psychiatric disorders are stuck in the first stage of disease discovery because while they are associated with particular symptom clusters, their etiologies have not yet been identified.[28] Reaching this second stage of disease discovery represents an "advanced state of knowledge" in which disease traits are viewed as legitimate and valid on the grounds that their etiologies are understood (Meehl 1977, 51). Advancing through this two-step process captures the "hard medical model" (Kendler 2012, 1) and the

[27] As Rosenberg states, "[d]isease begins with perceived and often physically manifest symptoms" (Rosenberg 1992, 310).

[28] Many "physical" medicine diseases are also stuck in this first stage in the sense that their etiologies are not understood (or are poorly understood). Examples of these diseases include systemic lupus erythematosus (SLE), Bell's palsy, and acrocyanosis.

standard view in medicine that "symptoms should be traced to underlying causal processes" (Murphy 2006, 107). These causal processes are often expected to be shared causal etiologies in the sense that originated with the germ theory model.

Conclusion

This paper has examined "the doctrine of specific etiology"—a principle that is said to underlie the nineteenth century germ theory model of disease. Not only is this principle associated with the success of this theory, but it is frequently cited as an important change in medical thinking that has influenced modern theories of disease. Despite these claims, it is not clear what types of specificity this doctrine refers to, why exactly these specificities matter, and how (if at all) they have influenced modern medicine. This paper has provided an analysis that addresses these points. I have suggested that the nineteenth century germ theory model involves two types of specificity at the level of causal etiology, and that these led to a conception of "shared causal" etiology that continues to figure in medicine today. This conception represents our modern understanding of etiology, and as etiology influences how diseases are classified, defined, and discovered, we see the influence of germ theory in all of these projects. Germ theory differs from earlier theories of disease in that it selects factors as causes when they provide control over disease outcomes. Of course, identifying factors with control over disease outcomes supported common goals of nineteenth century research communities such as treating, predicting, and curing diseases. It should be unsurprising that these features of germ theory have persisted because we have similar goals in modern medicine and these methods serve them well.

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