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Universal etiology, multifactorial diseases and the constitutive model of disease classification

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ABSTRACT

Infectious diseases are often said to have a universal etiology, while chronic and noncommunicable diseases are said to be multifactorial in their etiology. It has been argued that the universal etiology of an infectious disease results from its classification using a monocausal disease model. In this article, I will reconstruct the monocausal model and argue that modern 'multifactorial diseases' are not monocausal by definition. 'Multifactorial diseases' are instead defined according to a constitutive disease model. On closer analysis, infectious diseases are also defined using the constitutive model rather than the monocausal model. As a result, our classification models alone cannot explain why infectious diseases have a universal etiology while chronic and noncommunicable diseases lack one. The explanation is instead provided by the Nineteenth Century germ theorists.

1. The causes of disease

Multifactorial thinking pervades modern epidemiology and medicine, from the way we describe modern diseases as having multiple and variable etiology (Krieger, 1994; McMahon, Pugh, & Ipsen, 1960; Susser, 1985) to the way that we measure causal risk factors for diseases and customize medical classification, prognosis and prevention based on those risk factors (WHO, 2005; 2014). Nancy Krieger argues that "notions of multiple causation and multivariate analysis are so commonplace and so embedded in modern epidemiologic reasoning that they hardly merit discussion as a model or as an approach to understanding disease" (1994, pp. 891). As an example of multifactorial thinking, the major modifiable risk factors for cardiovascular disease, including stroke, are: smoking, obesity, physical inactivity, dyslipidemia, hypertension, diet and diabetes mellitus (Hennekens, 2015). Individually causal risk factors are not sufficient for disease (not everyone who smokes has a stroke); nor are they necessary (not everyone who has a stroke smokes).[1]

It is not only cardiovascular diseases like stroke and heart attack that are multifactorial, but also chronic diseases like diabetes and dementia, injuries like bone fracture, and even symptoms like back pain. The rise in prominence of multifactorial diseases is partly explained by medicine's own success in controlling infectious diseases and other acute health conditions (WHO, 2015). People are living longer and are increasingly afflicted with chronic diseases and noncommunicable diseases (NCDs) as they age (WHO, 2011; 2015). Chronic and noncommunicable diseases are now the leading killers worldwide, and are paradigmatically multifactorial in their causation.

The multifactorial etiology of modern ailments only seems noteworthy when set against a historical background. In the late Nineteenth and early Twentieth centuries, the paradigm medical maladies were infectious diseases, which are often described as having a single universal etiology. Particular infectious diseases are caused by a particular germ. The particular germ is even necessary for the particular disease; without variola virus, one cannot contract smallpox.

Alex Broadbent (2009; 2013; 2014) calls this turn-of-the-Twentieth Century understanding of diseases the "monocausal disease model" to emphasize the privileging of one particular cause. In contrast, the model of disease popular among epidemiologists and public health authorities beginning in the second half of the Twentieth Century is a "multifactorial model" that recognizes the contribution of multiple causal risk factors to the development of each type of disease. Broadbent argues that the monocausal model is as much a model of definition as it is a model of discovery. Not only do scientists discover a specific cause of a specific type of disease, they define that specific disease as the disease produced by that specific cause.

Abbreviations: NCD, noncommunicable disease; TB, tuberculosis; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MTBC, *Mycobacterium tuberculosis* complex; HPV, human papillomavirus; RRP, recurrent respiratory papillomatosis

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[1] The epidemiologist Kenneth Rothman (1976) illustrated this relationship between etiologic factors and disease by using 'causal pie' diagrams. In Rothman's diagrams, complete causal conditions are pies, individual etiologic factors are slices, and alternative pies can cause the same disease.

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The model of nosology or disease taxonomy that the monocausal ideal is thought to have supplanted is one in which types of disease were defined constitutively, in terms of the components that comprised them.[2] In the early Nineteenth Century, these components were typically symptoms, but by the middle of the Nineteenth Century they often included pathological anatomical lesions (Porter, 2002; Carter, 2003). For the simple reason that different causes can give rise to the same symptoms and lesions, the causes of these diseases were not singular and universal but multiple and variant. From this perspective, it looks like modern epidemiology and medicine have been dragged back to an era when disease etiology was multifarious, complex and unwieldy. The long and eclectic lists of etiological factors in early Nineteenth Century medicine exasperated the famous physician Jacob Henle, who called for the discovery and reporting of causes of disease that were "universal, necessary and sufficient" (Carter, 2003, pp. 25).

According to Codell Carter (2003), the monocausal model, which he calls "the etiological standpoint", came to characterize modern Western medicine beginning in the late Nineteenth Century. The story often goes that a monocausal understanding of infectious diseases allowed for breakthroughs in their treatment and prevention (Carter, 2003; Evans, 1993). Jeremy Greene and colleagues write: "Motivated by breakthroughs in cellular pathology, pathophysiology, and especially bacteriology, doctors increasingly came to see diseases as specific entities, each with its own specific causes, manifested as characteristic syndromes. This new model prompted doctors to seek therapies tailored to the disease and not the patient", a "therapeutic revolution" (2012, pp. 1080).[3] Thus, it is perhaps a letdown that many modern diseases are multifactorial and not monocausal.

In this article, I will reconstruct the monocausal disease model and ask why modern multifactorial diseases refuse to conform to the monocausal pattern. I will argue that multifactorial diseases are defined according to a constitutive model of classification, which explains why they are multifactorial. However, I will propose that – contrary to popular opinion – we can also understand the classification of infectious diseases according to the constitutive model. As an upshot, our classification models cannot fully explain the difference between those diseases with a specific universal environmental cause and those diseases without one; it is an old idea, the germ theory, that partly explains why infectious diseases have a universal etiology.

2. The monocausal ideal

According to Carter, "The etiological standpoint can be characterized by the belief that diseases are best controlled and understood by means of causes and, in particular, by causes that are *natural* (that is, they depend on forces of nature as opposed to the wilful transgression of moral or social norms), *universal* (that is, the same cause is common to every instance of a given disease), and *necessary* (that is, a disease does not occur in the absence of its cause)" (2003, pp. 1). The first criterion, the requirement that the cause of the disease is natural, immediately suggests a strategy for *discovering* a disease's etiology: empirical research, especially research in the natural sciences. Meanwhile, the third criterion, the criterion that the cause of the disease is necessary, suggests a principle for *defining* a disease category: one should define the disease according to the cause that was discovered. (The third criterion implies the second criterion of universality: if a certain cause is necessary for the disease, then that cause will always occur whenever the disease occurs.)

The etiologic standpoint is an ideal that Carter and many other authors believe guides etiologic research and faithfully describes our paradigmatic infectious diseases. Epidemiologist Mervyn Susser argues that Nineteenth Century discoveries by Pasteur and Koch "led to the redefinition and reclassification of many disease entities [disease types] by the criterion of cause … By current definition, tuberculosis is caused by the tubercle bacillus" (1973, pp. 23). Similarly, Rothman claims: "Necessary causes are often identifiable as part of the definition of the effect. For example, … infection with the tubercle bacillus is a necessary cause for tuberculosis" (1976, pp. 588). And philosopher Caroline Whitbeck notes that after the success of the germ theory in the Nineteenth Century "the name of the disease came to reflect the type of entity thought to cause it, the so-called etiologic agent, and etiology soon came to be definitive (i.e., to be regarded as essential) for those diseases for which it was known" (1977, pp. 622).

More recently, Alex Broadbent (2009; 2013; 2014) has referred to this principle of disease classification as the "monocausal model". He too emphasizes that "[t]he special status that the monocausal model offers to certain causes is not an empirical status, but a conceptual one. Certain causes *define* the disease in question" (2013, pp. 156). According to Broadbent's reconstruction, the monocausal model places a necessity requirement on the defining cause: "putative cause C is a cause of every case of disease D" (2003, pp. 150). Adopting this requirement, we can represent the monocausal model as follows:

a is case of disease *D only if* an *E* caused *a*.

In a case of infectious disease or poisoning, *E* refers to a specific etiologic agent (a specific germ or a specific toxin, respectively); in a disease of deficiency, it instead refers to the *absence* of a specific agent like a specific nutrient. The two key features of *E* – and thus of the monocausal model – are *causal specificity* and *causal necessity*. *E* is specific because it refers to one particular kind of causal agent; it cannot refer to a disjunction of several kinds of etiologic agents, or else the disease would not be *mono*-causal. *E* is necessary because *D* only occurs if *E* caused it.

Presenting the monocausal model in the above form draws attention to its role as a model for *defining* particular disease types/taxa such as anthrax or typhoid fever. Applied to the example of anthrax, an instance of infection (*a*) is a case of anthrax (*D*) *only if* the germ *B. anthracis* (*E*) caused the infection. As a necessary cause, *E* is a cause of every instance of *D*. Although this necessity arises because *D* is defined in terms of *E*, we cannot define *D* in terms of just any factor. The factor we choose must be a cause of *D*.[4] Whether or not a particular factor is a cause of *D* is an empirical matter, to be settled through empirical research rather than by stipulation.

Although the condition that *E* caused *a* is necessary for *a* to be a case of *D*, it is not sufficient. *B. anthracis* can cause many things – an immune response in those who have been vaccinated against the bacterium, the death of livestock, public hysteria. These occurrences are not thereby cases of anthrax. As a model for defining diseases, the monocausal model as I have presented it is incomplete, yet the constraint that it places on disease classification – the requirement of defining disease types according to a specific cause – is mighty nonetheless.

Broadbent's reconstruction of the monocausal model places a second requirement on the defining cause, a circumstantial sufficiency requirement: "given certain circumstances, which are not sufficient to cause D, every occurrence of C causes a case of D" (2013, pp. 150).[5,6] As

[2] Paul Thagard (1999) calls the change from one organizing taxonomic principle to another principle "tree switching".

[3] Greene et al. (2012) note that this "therapeutic revolution" was more complicated than this simple story might suggest, and that new therapies often took decades to arrive.

[4] One who holds that diseases form natural kinds (e.g. Lange, 2007) might want to add that for our disease classifications to be natural we must choose the *right* causes. Whether or not diseases form natural kinds – and if so, how we go about defining diseases accordingly – is a further issue for another paper.

[5] J.L. Mackie (1965) calls circumstantially sufficient causal conditions "*minimally* sufficient conditions" to emphasize that they contain no idle parts; were any cause missing, then the remaining causes would no longer be sufficient.

[6] Broadbent (2009) offers a different formulation of the second requirement: "given certain circumstances, a *C*-event is not a cause of any ¬*D* event (i.e. other diseases or good

Broadbent (2009) notes, in the absence of any further requirement beyond necessity it is possible that more than one cause could satisfy the monocausal model. He provides the example of oxygen: oxygen is needed for the survival of the patient and is thus necessary for the patient's having (any) disease *D*. However, as a model for defining diseases, the monocausal model need not limit the number of potential causes that could in principle be used to define the disease; rather, it need only define the disease in terms of one of these potential causes, which it can do with only a necessity requirement.

One of Broadbent's motivations for including a circumstantial sufficiency requirement is to limit the number of causes that could satisfy the monocausal model to one. Yet it is not clear that a circumstantial sufficiency requirement can achieve this goal, at least in a non-artificial way. One factor likely to be found in the 'given circumstances' listed in a circumstantial sufficiency requirement is 'lack of a sufficient immune response'. Then we would define a disease like tuberculosis as 'the disease caused by *tubercle bacillus* given *lack of a sufficient immune response against the tubercle bacillus*', plus other circumstances. But now tuberculosis is defined in terms of at least two causes: the tubercle bacillus, and lack of a sufficient immune response against the bacillus. Why should we regard the 'tubercle bacillus' as *the* defining cause? Just because it is mentioned apart from the other causes in a 'necessity requirement'? This definition is logically equivalent to: 'the disease caused by *lack of a sufficient immune response against the tubercle bacillus* given *tubercle bacillus* … ' So, the only way that a circumstantial sufficiency requirement limits the number of causes satisfying Broadbent's monocausal model to exactly one is by choosing one of these two necessary causes to stand apart from all other causes in the definition of the disease.

Moreover, there are reasons to doubt that our current model of infectious disease classification includes a circumstantial sufficiency requirement. I will discuss these reasons in section 5 when I consider what we might gain by including circumstantial sufficiency requirement. In the meantime, my formulation of the monocausal model (represented above) will only satisfy Broadbent's necessity requirement. In including only the requirement that the disease is caused by a specific necessary cause, I capture a more minimal, widespread idea of the late Nineteenth Century, expressed by Carter (2003), Susser (1973), Rothman (1976) and Whitbeck (1977) above. To distinguish my rendering of the monocausal model from Broadbent's rendering (which includes both a necessity requirement and a circumstantial sufficiency requirement), I will occasionally refer to my version as the 'minimal monocausal model' and his version as 'Broadbent's monocausal model'. However, unless otherwise stated, the following discussion will apply to either version of the monocausal model.

3. The multifactorial disappointment

Many chronic and noncommunicable diseases resist the monocausal model in that they do not have a necessary environmental cause. Rather, they are recognized as diseases of multifactorial etiology. As a slogan, multifactorial diseases are those that have several causes, typically including genetic and environmental factors. Each case of the disease is caused by the interaction of multiple causes, and unique constellations of causes produce unique instances of the disease. High blood pressure and poor diet might interact to produce one case of stroke, while smoking and sedentary lifestyle might interact to produce another case.

So far, little distinguishes monocausal from multifactorial diseases. Monocausal diseases are also produced through causal complexes that may vary from case to case. For example, many individuals who are exposed to the tubercle bacillus develop latent tuberculosis infection but not active tuberculosis disease (TB). Progression from latent infection to active disease is in part caused by endogenous factors that vary among patients with active TB (Raviglione & O'Brien, 2012).

One feature that distinguishes so-called 'multifactorial diseases' like heart attack, stroke, osteoporosis and prostate cancer from monocausal diseases is that 'multifactorial diseases' lack a defining necessary cause. While smoking is a cause of each of the four diseases above, any of them can occur in the absence of smoking. In fact, the *only* feature that distinguishes 'multifactorial diseases' from monocausal diseases is their lack of a necessary cause. All that we can say about 'multifactorial diseases' at this point is that they are not monocausal.[7]

The fact that many chronic and noncommunicable diseases are not monocausal might seem unfortunate from a therapeutic perspective. It is tempting to award some credit to the monocausal model for medical breakthroughs like vaccines and antibiotics, which target the offending pathogen. In 1882, Robert Koch presented convincing evidence to the Berlin Physiological Society that the tubercle bacillus he had isolated was the cause of TB. One of the many esteemed attendees of the meeting was Paul Ehrlich, who later opined: "That evening was engraved in my memory as the most majestic event I have ever participated in" (quoted in Evans, 1993, pp. 21–22). Ehrlich went on to lead a research laboratory that synthesized the world's first effective and specific antibiotic: arsphenamine (Salvarsan), a treatment for syphilis.

If the monocausal model was so historically useful for infectious diseases, why don't scientists classify NCDs 'monocausally'? After all, they have discovered modifiable causal risk factors for most of them. A causal risk factor is part of a complex cause of an NCD, just as a germ is part of a complex cause of an infectious disease. Smoking is considered a 'risk factor' for cardiovascular disease because exposure to cigarette smoke confers a certain risk or probability of disease. But exposure to *Plasmodium* also imparts a specific risk of disease; and whether we are dealing with smoking and cardiovascular disease or *Plasmodium* and malaria the probability of disease given exposure is less than one. So, while one may argue that individually causal risk factors merely contribute to disease and are not sufficient for it, the same is true of infectious agents, and prima facie that does not stop medical scientists from applying the monocausal model to infectious diseases.

A more tempting explanation for why scientists do not classify a greater number of NCDs monocausally is that there simply are no modifiable necessary causes for most NCDs. Whitbeck (1977) and Carter (2003) suggest that some diseases – perhaps cancers – may not in principle be amenable to classification according to a universal cause. However, recall that the necessity and universality of a cause under the monocausal model is produced through stipulating that a certain type of disease is – *by definition* – caused by a certain type of etiologic factor. There are no necessary (nontrivial) environmental causes of noncommunicable diseases because NCDs are not classified according to environmental causes. It is not that we don't define NCDs monocausally because they have no necessary cause; rather, NCDs have no necessary cause because we don't define them monocausally.

As Broadbent (2013) argues, if we like we can simply redefine nonmonocausal diseases to make them fit the monocausal model. Redefinition may be required even for an infection. Before Koch isolated the tubercle bacillus, tuberculosis was understood symptomatically and

(*footnote continued*)
health)", pp. 303. This restriction helps to limit the number of causes satisfying the requirements of the monocausal model – ideally, to one – by ruling out any necessary causes of D that are also causes of other ¬D states. Unfortunately, it appears that infectious diseases do not adhere to such a requirement. Assuming that each type of infectious disease has as its defining cause a specific germ, the defining cause of an infectious disease is a cause of other non-disease states (for instance, it is a cause of an immune reaction in individuals with immunity). Therefore, in order to construct a model that plausibly represents infectious diseases I will not consider the (2009) version of Broadbent's second requirement.

[7] James McCormick writes that the term 'multifactorial', when applied to etiology, is a "tautology", and that what distinguishes multifactorial from infectious diseases is that multifactorial diseases "do not have a single necessary cause" (1988), pp. 104. Broadbent (2009) refers to this characterization of multifactorial diseases as "bare multifactorialism".

pathologically in terms of 'tubers' in the lungs. So defined, 'tuberculosis' had several infectious causes, and could occur in the absence of Koch's tubercle bacillus. It was only after Koch redefined tuberculosis in terms of the tubercle bacillus that the disease came to have a necessary cause (Carter, 2003).

Non-monocausal diseases can be made to fit the monocausal model if we are willing to shift the borders of disease categories. In redefining tuberculosis as an infection caused by the tubercle bacillus, certain states previously considered to be cases of tuberculosis were excluded from the newly reconstituted tuberculosis category. We could similarly redefine coronary artery disease (CAD) as a coronary artery stenosis caused by smoking ('CAD*'). Cigarette smoke would then become a necessary cause of CAD*, and preventing smoking would invariably prevent CAD*. Preventing smoking would do nothing to prevent a coronary artery stenosis that falls outside of the reconstituted CAD* category, but then again preventing exposure to the tubercle bacillus will do nothing to prevent symptomatically and pathologically similar infections that fall outside of the reconstituted tuberculosis category.

Redefining NCDs according to the criterion of cause may not be as tidy as redefining infectious diseases. In principle (and, prima facie, in practice), infections can be sorted into a set of causally defined categories that are generally mutually exclusive and collectively exhaustive. Because *Plasmodium* and *V. cholerae* rarely causally interact, a case of 'infection caused by *Plasmodium*' ('malaria') would rarely be a case of 'infection caused by *V. cholerae*' ('cholera'). Moreover, because the etiologic agent has been identified for most infections, few infections would be left unclassified. On the other hand, there is a substantial amount of causal interaction among the causal risk factors we have identified for NCD states. A case of 'coronary artery stenosis caused by smoking' might also be a case of 'coronary artery stenosis caused by sedentary lifestyle' if both causes contribute to the same case of coronary artery stenosis. Furthermore, for many NCDs there exist a number of patients that lack all known causal risk factors yet have the disease (D'Agostino et al., 2008). Classifying patients according to cardiovascular disease risk factors alone would leave a good number of cases of cardiovascular disease undiagnosed.

Notwithstanding this taxonomic untidiness, chronic and noncommunicable diseases are not quite as resistant to the monocausal ideal as we might have thought. In order to achieve a monocausal classification system for chronic and noncommunicable diseases, scientists could simply redefine these diseases according to specific causes. But they do not. The non-monocausal etiology of 'multifactorial diseases' thus results at least partly from our classificatory choices. This raises the question: what model *do* we use to define chronic and communicable diseases, and why does it result in 'multifactorialism'?

4. The constitutive model: chronic and noncommunicable diseases

For their stubborn defiance of a single cause model, chronic and noncommunicable diseases are often labeled as 'multifactorial'. In the early-mid 1800s, diseases were similarly recognized as having diverse causes, none of which were universally responsible for the disease (Carter, 2003). I explained that the reason for this multifactorialism was that diseases were defined constitutively, in terms of their component symptoms or pathological anatomical structures, and that several unique causal complexes can give rise to the same symptoms and anatomy. How can we explain modern day multifactorialism?

The answer is that like Nineteenth Century maladies, chronic and noncommunicable diseases are classified according to their constitution - what the disease is. For instance, chronic obstructive pulmonary disease (COPD) is often defined as "*a disease state* characterized by airflow limitation that is not fully reversible" (Reilly, Silverman, & Shapiro, 2012; my emphasis). Osteoporosis is defined as "*a bone density* that falls 2.5 standard deviations (SD) below the mean for young healthy adults of the same sex" (Lindsay & Cosman, 2012; my emphasis). Meanwhile, heart failure is defined by the American College of Cardiology Foundation as "*a complex clinical syndrome*" consisting characteristically of dyspnea, fatigue, edema and rales (Mann & Chakinala, 2015, pp. 1500; my emphasis).

Turning to the realm of cancers, "The World Health Organization (WHO) defines lung cancer as *tumors arising from the respiratory epithelium* (bronchi, bronchioles, and alveoli)" (Horn, Lovly, & Johnson, 2015, pp. 507; my emphasis). There are several subtypes of lung cancer, including small-cell carcinoma, which is defined as follows: "Small-cell carcinomas *consist of* small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, absent or inconspicuous nucleoli, and a high mitotic count" (Horn et al., 2015, pp. 507; my emphasis). In contrast, "mesotheliomas are *primary tumors that arise from the mesothelial cells* that line the pleural cavities" (Light, 2015, pp. 1717; my emphasis).

Not to neglect acute cardiovascular conditions, myocardial infarction is defined as "*myocardial necrosis* in a clinical setting consistent with acute myocardial ischemia" (Antman & Loscalzo, 2015, pp. 1602; my emphasis). Finally, "[a] stroke, or cerebrovascular accident, is defined as *an abrupt onset of a neurologic deficit* that is attributable to a focal vascular cause" (Smith, Johnston, & Hemphill, 2015, pp. 2559; my emphasis).

These examples illustrate a typical contemporary pattern: chronic and noncommunicable conditions are primarily classified according to what the condition is (e.g. a state giving rise to irreversible airflow limitation, a low bone density, a complex cardiac syndrome, tumors arising from respiratory epithelium, tumors arising from mesothelial cells, myocardial necrosis, abrupt onset neurological deficits), and *not* based on a specific etiologic agent. I will call this commonsensical taxonomic principle the *constitutive disease model*.

For diseases like COPD, osteoporosis, and small-cell lung cancer, the constitutive criterion is both necessary and sufficient.[8] We can thus represent the constitutive model as follows:

a is a case of disease *D* if and only if *a* is a *C*.

Applied to the example of osteoporosis, a bodily state (*a*) is a case of osteoporosis (*D*) if and only if *a* is a bone density that falls 2.5 standard deviations below the demographic mean (*C*). The key characteristic of *C* is *constitutive necessity*. *C* need not refer to a specific entity (it might, for instance, refer to a disjunction of factors), but – whatever *C* includes – *D* only ever occurs when *C* occurs. In small–cell lung cancer, *C* refers to a tumour derived from the respiratory epithelium of the lungs that has particular morphological characteristics. In COPD, *C* refers to an irreversible disposition towards airflow limitation.[9]

From the discussion so far, one might infer that our classification models on their own determine which diseases have a universal environmental cause. Infectious diseases have one because they are defined using the monocausal model, while chronic and noncommunicable diseases lack one because they are defined using the constitutive model. However, I will now argue that the monocausal model does *not* in fact describe the classification of infectious diseases, that the

[8] For other disease types or subtypes, the constitute criterion is only necessary and additional criteria are needed to define the disease. For instance, type I diabetes is defined as (i) a disorder of glucose metabolism that is (ii) produced by the autoimmune destruction of pancreatic beta cells (Powers, 2012). The definition of heart failure requires that the syndrome results from ventricular dysfunction (Mann & Chakinala, 2015). And in stroke the neurological deficits must be due to some focal vascular cause (Smith et al., 2015). So it is not the case that etiology or pathogenesis is irrelevant to disease classification.

[9] Aside from the question of which disease model medicine uses to define disease types, there is also an ontological question about disease tokens: what kind of a thing – object, state, process or other – is a disease (Simon, 2011)? Elsewhere (Fuller, 2017), I argue that chronic diseases are generally bodily states or properties. Some are dispositional (e.g. COPD is a state disposed towards obstructed airflow), while others are manifest (e.g. osteoporosis is a manifestly low bone density).

constitutive model instead describes infectious disease classification, and that the difference between those diseases with a specific universal environmental cause and those diseases without one cannot be explained by classification choices alone.

5. Constitutive model vs. monocausal model: infectious diseases

Carter calls the "etiological standpoint" (the monocausal model) "a defining characteristic of modern western thinking about disease" (2003, pp. 1). According to Carter, "[o]f the numerous changes that have occurred in medical thinking over the last two centuries, none have been more consequential" (2003, pp. 1). On the received view, the monocausal model came to define infectious diseases beginning in the late Nineteenth Century (Broadbent, 2014; Carter, 2003; Evans, 1993; Greene, Jones, & Podolsky, 2012; Stehbens, 1992; Susser, 1973; Whitbeck, 1977). But if ever the monocausal model (as characterized in section 2) was descriptive of infectious nosology, it is no longer. As the following problem cases illustrate, the monocausal principle does not classify or incorrectly classifies many important infections, while the constitutive model succeeds where the monocausal model stumbles. I conclude that infectious diseases are instead defined using the constitutive model; more specifically, they are defined according to the infection in which the disease consists.

The first set of problem cases includes infections that are not universally caused by the same unique pathogen, and thus are not classified according to the monocausal model because they violate the requirement of causal specificity. Certain infectious conditions or syndromes can be caused by a great many different germs. The common cold is caused by over 100 different viruses, and pneumonia is caused by several different types of microbe (Longo, 2012). While the monocausal model is usually described as a model of *diseases* (and syndromes are not diseases), we might have thought that its guidance extended to infections generally given its purported utility for infectious diseases. Yet some of the most common infections around do not adhere to its structure.

Even tuberculosis, an infectious disease that supposedly exemplifies the monocausal model, does not have a universal microbial cause. Robert Koch understood tuberculosis as a disease caused by the 'tubercle bacillus' (Evans, 1993). We now recognize TB as a disease caused by the "*Mycobacterium tuberculosis* complex (MTBC)" (ATS, 2000; Horsburgh, 2015; Raviglione & O'Brien, 2012). *Mycobacterium tuberculosis* is the species most commonly responsible for tuberculosis, especially in North America, but MTBC also includes other species of *Mycobacterium*, including *M. africanum* and *M. bovis*. It would be too nonspecific to say that tuberculosis is caused by *Mycobacterium* because certain mycobacteria cause other diseases instead. Rather, MTBC consists of a subset of mycobacteria. But how can we appropriately define this subset? If we define MTBC as the mycobacterium that causes tuberculosis, then defining tuberculosis as a disease caused by MTBC would be circular. If instead we defined MTBC as a disjunction of *M. tuberculosis*, *M. africanum*, and so on, then it is not clear that MTBC refers to a *specific* etiologic agent.[10] Tuberculosis is supposed to be our paradigm monocausal disease, yet it seems to violate the monocausal model's condition of causal specificity. Tuberculosis is not monocausal after all.

The constitutive model can handle these problem cases because causal specificity is not a constraint on the constitutive model. In medicine, all viral infections of the upper respiratory tract are defined as 'the common cold', and all infections of the alveoli of the lungs are defined as 'pneumonia'. The common cold and pneumonia are thus defined according to the state in which they consist: an infection of a particular part of the airway.[11] Similarly, as tuberculosis consists in an active infection with any one of the MTBC bacteria, the simplest way to group these infections together as instances of tuberculosis is to define 'tuberculosis' constitutively as an active infection with any one of these mycobacteria.

When I say that an infectious disease consists in an 'infection', I am referring to the state of being infected rather than the process of becoming infected. This allows us to say that tuberculosis, as infection with MTCB bacteria, is caused by MTBC bacteria; it amounts to saying that tuberculosis, the state of being infected with MTBC bacteria, is caused by exposure to MTBC bacteria or transmission of MTBC bacteria or the process of becoming infected with MTBC bacteria (I will further analyze these kinds of statements in section 6). It is also worth noting that the state of being infected with a microbe is not merely the state of having the microbe in or on one's body because uninfected people are colonized by microbes all the time. There are asymptomatic carriers of MTBC (who have 'latent TB'), as well as asymptomatic carriers of many other pathogenic microbes, including *Streptococcus pyogenes*, the bacterium responsible for strep throat. An infection with a germ is best understood as the state of having the germ manifesting itself in the body in a certain characteristic way, which distinguishes mere colonization with the germ (or being a carrier) from infection (or having the disease).

The monocausal model runs into further trouble in classifying opportunistic infections. In these cases, it *does* classify the infection according to a specific cause, but it does so incorrectly. Consider opportunistic infections in patients with HIV disease. Infections are opportunistic when they result from a compromised immune system. In patients with HIV disease, the immune system is compromised because HIV infects T cells, which normally coordinate the immune response. One relatively common opportunistic infection in patients with HIV disease is an active respiratory infection with *M. tuberculosis*. It seems reasonable to define 'HIV disease' according to the monocausal model: as an infection caused by HIV. Doing so would correctly classify the T cell infection as 'HIV disease'. But what about the respiratory infection?

As the respiratory infection was caused by *M. tuberculosis*, we could classify it as tuberculosis. However, the respiratory infection was also caused by HIV, which weakened the immune system and facilitated the opportunistic infection. Thus, we should also define the respiratory infection as 'HIV disease' according to our monocausal definition. Because infections with *M. tuberculosis* are unequivocally *not* cases of HIV disease, HIV disease must not be defined as an infection caused by HIV. Whenever one infection weakens the immune system, leading to a second infection, applying the monocausal model risks classifying the second infection incorrectly as the same disease as the first infection. Unfortunately, HIV infection can cause a wide range of opportunistic infections, so this problem for the monocausal model is not limited to *M. tuberculosis* infections. More generally, when two pathogens contribute to the occurrence of the same case of infectious disease, the monocausal model may have trouble determining which disease has occurred.

Another problem of misclassification described by Benjamin Smart (2014) is the case of human papillomavirus (HPV). HPV types 6 or 11 can cause rare infections like laryngeal papillomatosis and recurrent respiratory papillomatosis (RRP). The virus more commonly causes anogenital warts. If we define either laryngeal papillomatosis or RRP as an infection caused by HPV (type 6 or 11), then anogenital warts are misclassified as one of these two rarer conditions. Similarly, in addition

[10] It is not totally clear what constitutes a *specific* agent. Influenza can be caused by the influenza A virus, the influenza B virus, or the influenza C virus. Is 'the flu virus' then a specific cause? One plausible test of specificity is that we must be able to usefully define the etiologic agent without resorting to a logical disjunction for that agent to count as specific. For bacterial infections, another plausible test is that the agent must refer to a particular species of bacterium. At present, MTBC consists of multiple mycobacterial species.

[11] Rather than an infection, 'the common cold' and 'pneumonia' can refer to the symptoms caused by that infection. In this case, the common cold and pneumonia are still defined constitutively, but as a particular syndrome.

to causing strep throat, *Streptococcus pyogenes* occasionally causes a skin infection called erysipelas. Defining strep throat as an infection caused by *S. pyogenes* misclassifies erysipelas as strep throat. More generally, when a particular pathogen can cause more than one type of infectious disease, the monocausal model may again have difficulty sorting out which disease has occurred in a particular case.

When infectious diseases are defined constitutively, these problems of misclassification do not arise. On the constitutive model, HIV disease is roughly defined as an infection with HIV, while laryngeal papillomatosis is defined as a laryngeal infection with HPV type 6/7, and strep throat is defined as an oropharyngeal infection with *S. pyogenes*. Then an opportunistic *M. tuberculosis* infection that was caused by HIV immunosuppression is *not* HIV disease because it is not an HIV infection, while HPV infection of the anus or genitals is not laryngeal papillomatosis because it is not a laryngeal infection, and *S. pyogenes* infection of the skin is not strep throat because it is not an oropharyngeal infection.

To this point, I have been considering challenges to my particular version of the monocausal model, which defines the disease according to a specific necessary cause – the 'minimal monocausal model'. Before pronouncing the monocausal model dead, I will briefly consider whether Broadbent's (2013) version of the monocausal model fares better against the problems that I have identified. Broadbent's monocausal model includes an additional circumstantial sufficiency requirement, which specifies certain circumstances that – together with the necessary cause – are causally sufficient for the particular disease and that must be present for the condition to count as a case of that disease. Adding this requirement will do nothing to help with cases like pneumonia and tuberculosis in which the infectious condition is variably caused by different germs because the requirement that the disease is universally caused by a single specific factor remains in Broadbent's formulation.

However, a circumstantial sufficiency requirement *would* remedy the problem of secondary infections. Recall the example of HIV weakening the immune system, causing a secondary infection. The minimal monocausal model defines HIV disease as an infection caused by HIV, which applies (incorrectly) to the secondary infection. Broadbent's monocausal model could instead define HIV disease as the disease caused by HIV given certain specified circumstances that are causally sufficient for the disease (with HIV). This definition would not count a secondary infection with a germ like *M. tuberculosis* as HIV disease because the causes listed in the definition won't be causally sufficient for *M. tuberculosis* infection, or else any time HIV infection occurred *M. tuberculosis* infection would also occur (which it does not). Similarly, Broadbent's monocausal model is immune to the problems wrought by HPV and *S. pyogenes*. When we include circumstantially sufficient causes in the definition of laryngeal papillomatosis, the definition no longer incorrectly covers HPV warts of the anus and genitals, and when we include circumstantially sufficient causes in the definition of strep throat, the definition no longer incorrectly covers skin infections with *S. pyogenes*. Simply put, the circumstances that are causally sufficient for HPV warts of the larynx are not sufficient for HPV warts of the anus and genitals, while the circumstances that are causally sufficient for *S. pyogenes* infection of the throat are not sufficient for *S. pyogenes* infection of the skin.

Despite its success in overcoming these problems that confront the minimal monocausal model, Broadbent's circumstantial sufficiency requirement faces three important challenges that make it unlikely that any version of the monocausal model including the circumstantial sufficiency requirement could serve as our model for defining infectious diseases.

First, the gold standard diagnostic test for many microbial diseases is laboratory culture of the organism. If we can isolate *M. tuberculosis* from a patient showing symptoms of tuberculosis and grow the germ (which is not easy as it grows poorly in culture), we are then able to diagnose the patient with tuberculosis – nearly definitively. There is no need to demonstrate that certain other circumstantially sufficient causes were also present in order to make the diagnosis. Thus, it is unlikely that our current model of infectious disease classification includes a circumstantial sufficiency requirement.

Second, specifying the circumstances under which a germ is causally sufficient for a disease seemingly requires full causal knowledge. Broadbent (2009, 2013) recognizes this difficulty, and draws an analogy with laws of nature and their ceteris paribus conditions. It is often argued that laws of nature hold only 'ceteris paribus', or given certain circumstances. These circumstances will probably number greatly, and many of them will escape our knowledge. Arguably, this challenge is not a fatal one for scientific inference. Yet, while we might be able to get away without knowing all of the ceteris paribus conditions in scientific inference, it is not clear that we can get away without knowing all of the circumstantially sufficient conditions included in a disease definition in disease classification. Without explicitly specifying all of the circumstances, our disease definitions become partially elliptical and vague. Faced with a potential instance of the disease, we will not be sure whether it satisfies the definition because we will not be sure whether it satisfies all of the circumstantially sufficient conditions. But we *are* generally able to classify infections and do not generally confront vagueness in our infectious disease definitions. Any confusion we have is generally epistemic rather than conceptual in origin. Again, it is unlikely that our current model of disease classification includes a circumstantial sufficiency requirement.

Finally, specifying the circumstances to be included in a sufficiency requirement seems to demand that we have an independent means of picking out the cases we intend to include under our definition. For instance, say we define HIV disease as all and only those cases of disease that are caused by HIV, given specified circumstances X, where HIV plus X is causally sufficient for the disease. How do we decide what factors to include in X? If we want to exclude a secondary *M. tuberculosis* infection from 'HIV disease', then we have to make sure that the factors we include in X are not causally sufficient (given HIV) for secondary infections with *M. tuberculosis*. But then we have already decided that we do not want secondary *M. tuberculosis* infections to count as 'HIV disease'. To make that decision, we must have some other independent means of deciding which infections to include in the category 'infections for which HIV plus some X is causally sufficient' and which infections to exclude from that category. Causally sufficient circumstances can only be specified once we have identified the effect, not beforehand.

To summarize this final problem, the sufficiency requirement must specify X in order to define the disease, but this requires having some independent principle for identifying the infections (the effects) for which we want 'the germ plus some X' to be causally sufficient. First, we must use this independent principle of classification to pick out all the infections we want to include under our definition. Only then can we specify the circumstances that would be causally sufficient (given the germ) for those infections.

I have already suggested one independent principle: we can pick out all those cases that *consist in* HIV infection. Applying this condition would allow us to specify X: X is whatever factors are causally sufficient for HIV infection (given HIV transmission). However, this specification would be tedious, and likely incomplete (raising my previous worry). If we already have this independent principle for picking out all those cases we want to include under 'HIV disease' (namely, those cases that consist in HIV infection), it is more plausible to believe that we currently define HIV according to this condition, which I call the constitutive model.

The minimal monocausal model fails to classify or incorrectly classifies several important infections. While Broadbent's monocausal model, with its circumstantial sufficiency requirement, avoids some of these misclassification missteps, it incurs several additional problems. Neither version of the monocausal model best describes current infectious disease classification. In comparison, the constitutive model avoids these problems and classifies tricky cases consistent with how

they are actually classified by physicians. It does so quite simply by defining the disease according to the infection in which it consists.[12]

6. Implications

In summary, the constitutive model is the standard model of classification for modern diseases of all sorts – infectious, noncommunicable, acute and chronic. It sometimes appears as though an infectious disease *is* defined monocausally in the medical literature. For instance, *Harrison's Principles of Internal Medicine* (Longo, 2012) defines influenza as "an acute respiratory illness caused by infection with influenza viruses", and cholera as "an acute diarrheal disease … caused by *V. cholerae*". Yet as the problem of the opportunistic infection makes visible, monocausal classification risks misclassification. On a given occasion, the flu virus or cholera bacterium could be part of the complex causal history of any number of diseases. Perhaps the flu virus brought the patient in to hospital, where they subsequently contracted hospital-acquired bacterial pneumonia, and the pneumonia was thus an acute respiratory illness caused (indirectly) by the flu virus. Consequently, monocausal descriptions are best viewed as rough characterizations rather than as formal definitions. The practice of loosely defining infectious diseases monocausally might result from conceptual conflation of the cause of an infectious disease with the infectious disease's constitution.

We might wonder whether the monocausal model as I have described it was ever descriptive of infectious diseases, or whether the constitutive model ruled throughout the Nineteenth Century and into the Twentieth. If indeed the constitutive model operated throughout the microbiological revolution, then the dramatic shift in disease classification was not a change from an earlier 'symptomatic model' of distinguishing diseases based on their symptoms to a monocausal model of distinguishing diseases based on their cause. Instead, the shift was from the constitutive classification of diseases in terms of the observable (symptoms, and then anatomy) to the constitutive classification of diseases in terms of the theoretical and unobservable (microbial infections). What changed was not medicine's model of disease classification, but its conception of what diseases are, from a concept of diseases as clusters of signs and symptoms to a biomedical concept of diseases as theoretical biological entities.

As a further upshot of my thesis, we cannot understand the difference between a disease with a specific universal environmental cause and a disease without one as resulting solely from the application of different models of classification. Yet except for infections like TB (for which the etiologic agent is nonspecific), infectious diseases *do* have a specific universal environmental cause: a particular pathogen. Carter argues that "[c]auses are made universal and necessary by adopting suitable disease characterizations" (2003, pp. 110). Carter has the monocausal disease model in mind, and if the monocausal model were the standard model of disease classification then his claim would be both true and complete. Instead, in explaining the existence of universal causes under the constitutive disease model, suitable disease characterizations do only some of the work.

In part, the universal etiology of most infectious diseases arises because we typically define infectious diseases as infections with a specific germ. Koch's great contribution to medicine was not only in discovering that the tubercle bacillus causes tuberculosis or that *B. anthracis* causes anthrax, but also in defining tuberculosis as an infection specific to the tubercle bacillus and anthrax as an infection specific to *B. anthracis*. According to the constitutive model, anthrax is defined as an infection *with B. anthracis*.

When we say that the cause of a particular disease is its specific pathogen, one plausible interpretation of this statement is that the cause of that disease is environmental exposure to the specific pathogen or transmission of that pathogen to the host. It is indeed the case that anthrax is universally caused by exposure to *B. anthracis* in the environment. But the constitutive model does not necessitate this fact; it is not analytically true that anthrax is caused by environmental exposure to *B. anthracis*, as consulting the rough definition of anthrax above will show. It could have turned out that infectious diseases arise through spontaneous generation of the pathogen in vivo; such a possibility is not ruled out when we define infectious diseases constitutively. In fact, certain infectious diseases are *not* caused by environmental transmission of the germ. Candidiasis, for instance, is due to overgrowth of the Candida yeast, which is part of our normal microbiome but can proliferate and manifest as an infection due to antibiotic use or immune compromise (when it infects the oral cavity it is called 'oral thrush', when it infects the vagina it is called a 'yeast infection').

It is a synthetic fact that anthrax is always caused by transmission of *B. anthracis* from without, an instantiation of a more general law that was discovered by the Nineteenth Century germ theorists: (almost all) infections arise through the transmission of a microscopic germ from environment to host (Louis Pasteur called this idea the "hypothesis of the dissemination of germs" (Carter, 2003, pp. 66)). The universal etiology of an infectious disease is partly explained by how we define the disease (as consisting in an infection with a specific germ), but is also partly a brute fact about the way that infections are acquired, a theoretical (rather than analytic) truth about their causation.

As the history of infectious diseases shows, identifying a universal etiology is partly a matter of discovery. Thus, the possibility remains of discovering a universal cause for some of our chronic and noncommunicable diseases under the constitutive model – the monocausal model is not the only route to universality. For instance, a combination of epidemiologic and laboratory research revealed that smoking is a nearly universal etiologic factor for small-cell lung cancer, and that asbestos is a nearly universal cause of pleural mesothelioma (Kumar, Abbas, & Aster, 2015). Classification is essential to this process of discovering universal causes. Without the proper taxonomic distinctions between malaria and dengue fever, transmission of *Plasmodium* via mosquito bites is not a universal cause of malaria. Similarly, without just the right analytic distinctions between small-cell carcinoma, pleural mesothelioma, and other malignancies of the lung and chest cavity, smoking is not a nearly universal cause of small-cell lung cancer and asbestos is not a nearly universal cause of pleural mesothelioma. Both discovery and classification have a role to play in the quest for the universal cause.

7. Conclusion

The monocausal disease model is often thought to have initiated a revolution in our conception of diseases at the turn of the Twentieth Century. Chronic and noncommunicable diseases, our modern multifactorial scourges, are thought to defy the monocausal ideal. But because causal necessity in the monocausal model is a matter of stipulation rather than discovery, chronic and noncommunicable diseases are non-monocausal by definition rather than by their nature. On closer inspection, even infectious diseases elude the monocausal model. Instead, modern diseases adhere to a constitutive model of classification. Thus, the universal etiology of infectious diseases is partly a theoretical truth and not solely an analytic consequence of the

[12] Broadbent (2009, 2013, 2014) proposes a Contrastive Model of disease classification as a corrective to the monocausal model. In the Contrastive Model, cases of a particular disease are defined through a causal contrast with a group of controls. According to Broadbent, "The Contrastive Model is prescriptive, not descriptive" (2014, 253). Similarly, as an alternative to the monocausal model Smart (2014) proposes a causal classification of diseases (CCD) in which the disease is defined according to its 'full cause'. Smart describes the CCD as an "ideal model of disease individuation" for achieving unique causal classifications for cases of disease (267, 2014). In comparison to these two models, my constitutive model is a *descriptive* model of disease classification, an attempt to describe contemporary disease categories. Thus, it is not in direct competition with either the Contrastive Model or the CCD. While it would be interesting to see whether the Contrastive Model and the CCD are susceptible to my criticisms of the monocausal model, investigating this question would take us too far off our main path.

classification models that we use. The monocausal model is not the only route to universal causation.

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