

Studies C (Forthcoming); post-referee eprint

Koch's Postulates: An Interventionist Perspective*

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Abstract. We argue that Koch's postulates are best understood within an interventionist account of causation, in the sense described in Woodward (2003). We show how this treatment helps to resolve interpretive puzzles associated with Koch's work and how it clarifies the different roles the postulates play in providing useful, yet not universal criteria for disease causation. Our paper is an effort at rational reconstruction; we attempt to show how Koch's postulates and reasoning make sense and are normatively justified within an interventionist framework and more difficult to understand within alternative frameworks for thinking about causation.

1 Introduction. Koch's criteria for disease causation, commonly referred to as "Koch's postulates," are often considered the first reliable method for establishing that a contagion is the cause of a disease. While Koch developed these criteria in the latter half of the 19th-century, they continue to receive significant attention. Koch's postulates are mentioned in nearly all beginning microbiology textbooks and they continue to be viewed as an important standard for establishing causal relationships in biomedicine

In the secondary literature, Koch's postulates are commonly represented in the following three-part form:¹

1. The contagion occurs in every case of the disease.
2. The contagion does not occur in other diseases or non-pathogenically.
3. After being fully isolated and repeatedly grown in pure culture the contagion can induce the disease by being introduced into a healthy animal.

* We would like to thank Jim Lennox, K. Codell Carter, Christoph Gradmann, and two anonymous reviewers for very helpful feedback on this work.

¹ (Carter 1987b; Evans 1976; Falkow 2004; Fredericks and Relman 1996, xviii). In correspondence, Carter has drawn our attention to his discussion on p. 136 of his (2003) in which he describes Koch's 1884 paper on tuberculosis as containing the most complete description of Koch's postulates. From this paper Carter extracts five "steps" which he takes Koch to advocate for "proving causation." Four of these steps (labeled Rt1, 2, 4, and 5) largely coincide with the three postulates cited above, but one (Rt3) ("The distribution of organisms must correlate with and explain the disease phenomenon") goes beyond 1-3 above. We focus on 1-3 because these are the most common form in which Koch discusses his criteria and also the most common form in which his postulates are discussed in the secondary literature.

Other formulations split the third postulate into two (Grimes 2006; Schaffner 2009) or add a final postulate requiring that the contagion be re-isolated from the diseased animal model and grown again in pure culture (Engelkirk, Duben-Engelkirk, and Wilson Burton 2011; Hogg 2013).

Formulating a version of Koch's postulates that reflects what he actually says is complicated by the fact that Koch rarely discusses his causal criteria explicitly and, when he does, they are not stated as generally or clearly as the postulates ascribed to him today.^{2,3} These features partly explain why there are so many different formulations of his postulates in the secondary literature and why those who analyze his criteria rarely cite his original publications (Carter 1985, 353). In our view, Koch's criteria are best understood through his detailed discussion of specific laboratory techniques, and experimental results, on which he relies to argue for causality.

Most scholars interpret Koch's postulates within a framework in which causal claims are understood as claims about necessary and sufficient conditions. This is the interpretation favored by K. Codell Carter, considered the "foremost authority" in this area (Gradmann 2009, 83), and most other historians and philosophers (Broadbent 2009; Smith 2001; Smith 2007). Within this approach, the first postulate is equated with the claim that the contagion is necessary for the disease, and the second and third with the claim that the contagion is sufficient for the disease.⁴ In Carter's formulation, "[a] phenomenon C is necessary for a phenomenon E if the nonoccurrence of C ensures the nonoccurrence of E" and "a phenomenon C is sufficient for a phenomenon E if the occurrence of C ensures the occurrence of E" (Carter 1985, 353-4)⁵. Carter uses this framework to analyze Koch's causal criteria throughout his publications and to argue that Koch relies on different criteria at different points in his work (Carter 1985, 354). He claims that Koch's early work begins with a conception according to which causation requires that the contagion is necessary for the disease and only later introduces the requirement that the contagion must also be sufficient. According to Carter, Koch relies on both necessity and sufficiency as criteria for causation in his

² In fact, the designation of these criteria as "postulates" did not originate with Koch himself, but with his student Friedrich Loeffler (Gradmann 2009, 3, 238; Gradmann 2008, 219; Brock 1988, 180-181; Loeffler 1884). In this paper, we refer to Koch's causal criteria as "Koch's postulates," as is common in discussions of his work, despite the fact that he did not use this terminology.

³ The fact that Koch rarely provides explicit discussion of his criteria has led some to claim that his publications contain "no original reference" for our modern day understanding of Koch's postulates and even that "Koch himself phrased no such postulates" (Gradmann 2008, 218).

⁴ (Carter 1987b, xviii; Smith 2007, 95-96; Smith 2001, 21).

⁵ In his (2003) Carter argues that causation is a "theoretical" notion and that "in the absence of an accepted theory no amount of empirical evidence can demonstrate causal relations" (p.196). He takes this to be Koch's view as well. Carter informs us (personal correspondence) that on this basis that he would reject any necessary and sufficient condition conception of causation as philosophically inadequate. He also holds that Koch is not committed to such a conception. We are not sure how to reconcile these remarks with the passages quoted above. In any case, as observed above, a number of other writers do hold interpretations of Koch's postulates in terms of necessary and sufficient conditions. The general issue of whether (apart from what Koch may have thought) causation is a "theoretical" or "non-empirical" notion (or whether this contrast a fruitful one) is beyond the scope of this paper.

mid-to-late 1880's publications and this is where we first see the "criteria we now know as Koch's Postulates" (Carter 2003, 134).

This common interpretation raises a number of puzzles. First, if Koch relies on different causal criteria throughout his work, why does he often state that he has used the same method throughout, which he claims to have introduced in his first publication on disease causation? Second, if Koch's postulates amount to requiring that a contagion is a necessary and sufficient condition for the disease, why does he describe such evidence as only establishing correlation, which he claims can be distinguished from causation with evidence from animal inoculation experiments? Relatedly, why would Koch require that his causal proof involve experiments demonstrating disease in animal models when he knew some contagious diseases lacked such models?

Independent of these interpretive issues, Koch's postulates seem useful for some diseases, but of limited use for others. As often noted, they cannot establish causation for diseases with causes that cannot be isolated in pure culture, that are present in healthy carriers, and that have no known animal model.⁶ Furthermore, it is often claimed that the postulates represent a "mono-causal" model that fails to accommodate the causal complexity characteristic of many diseases.⁷ While discussions of Koch's postulates often emphasize these limitations, they are also viewed as an important guide and "standard" for establishing causality (Fredericks and Relman 1996, 18). They are seen as establishing causality when they can be fulfilled and as a starting point for new and improved causal criteria when they cannot be.⁸ These discussions lead to the additional puzzle of how Koch's postulates can be useful, yet not universal.

In this paper, we argue that Koch's postulates are best understood within an interventionist account of causation, in the sense described in Woodward (2003). We describe how this interpretation is supported by Koch's discussions of disease causation, the causal reasoning he employs, and important aspects of the historical context within which he conducted his work. We view our paper as an effort at rational reconstruction; we attempt to show how Koch's postulates and reasoning make sense and are normatively justified within an interventionist framework and more difficult to understand within alternative frameworks for thinking about causation. Our discussion proceeds as follows: in section two, we discuss the historical context surrounding Koch's work and how it influenced his method of establishing disease causation. In section 3 we describe Woodward's (2003) interventionist account of causation and examine its relation to Koch's animal inoculation experiments, which comprise the third postulate. Section 4 discusses the relationship between interventionism and necessary and sufficient conceptions of causation in the context of understanding Koch's work. Section 5 argues that the first and second postulates are best understood as assumptions about *causal specificity*, a notion which plays an important role in Koch's causal reasoning. Section 6 provides more details regarding Koch's reasoning throughout his publications and how this is best understood with an interventionist framework.

⁶ (Smith Hughes 1977; Evans 1993).

⁷ (Broadbent 2009).

⁸ For examples of suggested modifications of Koch's postulates, see: (Falkow 1988; Evans 1976; Fredericks and Relman 1996; Smith 2001).

2 Historical Background.

2.1 19th Century theories of disease and contagia. In the early to mid-19th century, the European medical community remained significantly divided over the nature of disease causation. Some favored a miasmatic theory which maintained that diseases were caused by noxious airs or “miasmata” that emanated from putrid or decaying substances (Smith Hughes 1977, 1). These miasmata were characterized as undetectable, immaterial, and capable of causing diseases that seemed to be highly contagious and transmitted by air. Explanations for seemingly communicable diseases often appealed to “miasmatic influences” in addition to other long lists of causal factors, including dietary excess, exposure to extremes of temperature, emotional disturbance, and even the transgression of moral or social norms (Carter 2003; Smith Hughes 1977). Different diseases were often explained by citing similar lists of causal factors and the diseases themselves were characterized by groups of overlapping symptoms.

The miasmatic view contrasted with a contagionist theory of disease, which held that communicable diseases were caused by small material pathogens. The applicability of the contagionist theory to human disease was supported by evidence that certain plant and animal diseases were caused by microscopic contagia and that similar microscopic particles were present in some human diseases.⁹ Jacob Henle, a German anatomist and professor to Koch, was one of the earliest and most well-known supporters of the contagionist theory. Although Henle favored this theory, he admitted that there was insufficient evidence to conclusively support it as an account of human disease (Henle 1961). Like most others at the time, he viewed the observation of an association between microscopic matter and disease as inconclusive evidence of a causal relationship, because it was consistent with the microscopic matter being a secondary effect of some alternative disease cause. In his 1840 book “On Miasma and Contagia,” Henle discussed this “mere association” objection and specified a hypothetical experiment that could conclusively establish causality. He wrote:

If it was possible with our present-day methods to solve the question of the nature of the contagium through *direct observation*, then the theoretical discussion which I have advanced as proof would be superfluous and unnecessary. Unfortunately it must be predicted that *a right proof from positive observations is not yet possible*, even if these observations were more favorable to our hypothesis than the current ones. If one finds living, moving animals or distinct plants in the infectious (contagious) material, it is quite possible that these could have developed incidentally when this material was exposed to air. And even if the animals or plants in this contagious material were always present within the body, *there would still be the possible objection, and one hard to oppose*, that they are only parasitic, although constant elements, which develop in the body fluids and are significant for the diagnosis of the disease, without being the causal material or the seeds of the causal material. *In order to prove that they are really the causal material*, it would be necessary to isolate the animal seeds and animal fluid,

⁹ For example, in 1835 Augustino Bassi provided evidence that muscardine disease of silkworms was fungal in origin and in 1839 Johann Lucas Schonlein discovered the parasitic fungus thought to be responsible for “Impetigines” (Bulloch 1938, 395; Smith Hughes 1977, 2).

the contagious organism and contagious fluid, and then observe especially the power of each one of these to see if they corresponded. This is an experiment which cannot be performed (Brock 1999, 78; emphasis added).

While Henle viewed the observed association between bacteria and disease as insufficient to establish causation, he described a hypothetical experiment that could. This experiment involved separating the candidate contagion from the infectious material of a diseased organism, so that the causal influence of each could be observed separately and then attributed to the proper substance. Although Henle stated that this experiment could not be performed, its similarity to Koch's postulates has led many to claim that the postulates originated with Henle's work, which is why they are sometimes called the "Henle-Koch postulates" (Evans 1976). Like Henle, Koch was strongly influenced by the common objection that bacteria were merely associated with, and not causally relevant to, some diseases.

The contagionist theory that Henle supported in 1840 was quickly overshadowed by the cellular pathology approach that would dominate German medicine until the 1870s (Ackerknecht 1953, 105). This approach was popularized by Rudolph Virchow and viewed disease as a disturbance of internal cellular pathology and ultimately "a cell-based physiological process...where the constitution of the host played a dominant role in the manifestation of the disease" (Smith Hughes 1977, 22). While cellular pathology was not in direct conflict with the contagionist theory, it was poorly suited to elucidate the role of bacteria in disease, because it prioritized internal pathological causes over external factors like bacteria (Ackerknecht 1953, 106; Gradmann 2009, 43). For some diseases, pathological disturbance was thought to precede the presence of pathogenic bacteria, so that the internal pathology was viewed as the primary cause of the condition. For other diseases, it was claimed that different bacteria resulted in the same cellular pathology, so the shared pathological disturbance was viewed as the main or significant cause of the disease (Mazumdar 1995, 77). Cellular pathology would remain the focus of studies on disease causation until advances in botany, bacteriology, and animal experimentation would draw attention back to the contagionist approach.

With increasing evidence that microscopic contagia were likely causes of certain plant and animal diseases, research into microscopic life forms was considered increasingly relevant to studies of disease causation. This early work in bacteriology grew out of botanical research, with early studies of single-celled algae and the classification of bacteria as microscopic plant forms (Mazumdar 1995). During this time botanical researchers strongly disagreed about whether bacterial organisms were capable of transforming into different types or remain fixed as unchanging species. The transformationist position was supported, most notably, by the Swiss botanist Carl von Nägeli and strongly opposed by the German botanist Ferdinand Cohn (Mazumdar 1995, 42). Cohn proposed a Linnaean classification of bacteria, which divided them into fixed species similar to other plants and animals. The unresolved debate between transformationist and fixed-species views complicated attempts to clarify the relationship between bacteria and disease. If bacteria could cause disease, but also spontaneously transform between species, it was not clear how to study which bacterial "types" or "forms" were the cause of disease. Transformationist theories implied the impossibility of isolating and studying single bacterial species and meant that some diseases could be attributed to large groups of inter-transforming bacteria.

2.2 Koch's studies of disease causation. Koch began his work on disease causation in 1873 and published the majority of his work between 1876-1890 (Brock 1988; Gradmann 2009). While he would ultimately publish over 100 papers throughout his lifetime, 10 of these papers are typically the focus in analyses of his criteria of disease causation.¹⁰ These papers can be roughly divided into three groups, which chronologically track Koch's work on anthrax, tuberculosis, and cholera, respectively.¹¹

Koch began his work on disease causation at a time when there was widespread interest in controlling and preventing the devastating effects of various diseases and increasing support for the view that such diseases might have bacterial etiologies. Within a scientific community that had an increased interest in bacterial causes, but polarizing disagreements about the fixed-species nature of bacteria, Koch's work in this area began with a careful study of bacterial life forms. In his earliest work on anthrax, he created novel techniques for isolating, identifying, and visualizing bacteria. In the beginning of his first publication on disease causation, he describes how he used these techniques to identify a single fixed-bacterial species in anthracic animals—*Bacillus anthracis*—and how he traced the entire life-cycle of this bacilli, including its spore-forming stage, for the first time. This identification of a single bacterial species that is associated with a particular disease is characteristic of his approach toward establishing causality—it persists throughout his work on disease causation and is reflected in his first two postulates. He was likely motivated to focus on this as natural first step since it provided evidence of the presence and stability of a single microbial species in disease, at a time when both of these were questioned by his research community.

However, while evidence of association between bacteria and disease was suggestive of causation, Koch viewed this evidence as insufficient to establish such a relation. In a manner similar to Henle's hypothetical experiment, Koch conducted animal inoculation experiments with pure cultures of anthrax bacilli to establish that they were the cause of anthrax disease. He modified this experimental practice by identifying superior animal models and inoculation sites, developing sterile techniques, and advancing procedures for isolating pure cultures of bacteria. He used these techniques to demonstrate that inoculation of the anthrax bacilli "invariably" caused disease, while inoculation of bacilli-free controls did not, evidence which he viewed as providing "sufficient proof that the spores of *Bacillus anthracis* cause anthrax" (Koch 1987a, 12). This step is reflected in the third postulate, which involves isolating the contagion and inoculating it into an animal model to reproduce the disease of interest. In his later work on tuberculosis Koch uses the same isolation and inoculation steps, which he claims to have introduced in his anthrax research (Koch 1987d). Koch's view that association is insufficient to establish causation and that inoculation experiments are highly important for such determinations can be seen in his 1884 work on tuberculosis. Koch writes:

From my numerous observations, I conclude that these tubercle bacilli occur in all tuberculous disorders, and that they are distinguishable from all other microorganisms. *From the simultaneous occurrence of tuberculous disorders and bacilli,*

¹⁰ These 10 papers have been translated from German into English by K. Codell Carter (Koch 1987a-g).

¹¹ In addition to these diseases, one of these papers examines the etiology of infectious wound diseases.

*one cannot conclude that they are causally related...*To prove that tuberculosis is caused by the invasion of bacilli, and that is a parasitic disease caused by the growth and multiplication of bacilli, it is necessary to isolate the bacilli from the body, to grow them in pure culture until they are freed from every disease product of the animal organism and, by introducing isolated bacilli into animals, to reproduce the same morbid condition..(Koch 1987d, 82, emphasis added)

This passage suggests the importance Koch placed on his animal inoculation experiments, which he viewed as having a “great significance” and as the “weightiest aspect of his proof” (Koch 1987e, 141; Koch 1987b; 117). The importance Koch placed on this work makes sense when it is understood how he relied on such experiments to distinguish causal from correlational relationships. The role of these experiments in Koch’s postulates and the rationale behind their use are captured by the interventionist account of causation which we describe in the next section.

3 The interventionist framework.

3.1 Interventionism and Koch’s third postulate. The basic idea of interventionism is that causal relationships are relationships that are potentially exploitable for manipulation and control: if you can intervene on C in such a way that changes in C are reliably associated with changes in E, then C causes E. Conversely, if C causes E and appropriate interventions on C are possible, then these should be followed by changes in E. (Woodward 2003). More specifically, we have the following necessary and sufficient condition for causation, where C and E are types of events:

(M) C causes E if and only if (i) there is some possible intervention on C such that (ii) were this intervention to occur, there would be an association or correlation between C and E.

A number of features of (M) require additional clarification. First, the notion of an *intervention*: this is explained in more detail below, but heuristically one may think of it as an idealized experimental manipulation of C which is appropriately *unconfounded* for the purposes of determining whether C causes E. In this context, a confounder can be understood as some additional causal factor C* that may be responsible for the presence of an association between C and E and that makes it look as though C causes E, even though it does not. The idea behind (M) is that the intervention gives C an independent causal history in a way that removes the potential confounding influence of other factors that might be responsible for the presence of an association between C and E. In particular, the intervention produces a change in C that is uncorrelated with such confounders, thus ensuring that if an association between C and E is present when the intervention on C occurs, that association can only be due to the causal influence of C on E. One motivation for (M) is that it captures the common sense methodological idea that an appropriately unconfounded experimental manipulation of C is an especially reliable way of determining whether C causes E.

In the present context we are dealing with binary variables that represent whether some candidate cause C for some disease D, is present or absent and the effect is the disease itself, which will also either be present or absent. In this case, an intervention “on” C would involve introducing

C, in the uncorrelated or unconfounded manner described above, into some particular context. For example, this might involve introducing C into an animal's blood system in which it was previously absent (i.e., changing its value from "absent" to "present") or removing it from a context in which it was previously present (changing its value from "present" to "absent"). According to interventionism, C causes E if and only if such an intervention on C is associated with a change in the incidence of the disease, such as its presence or absence or the rate at which it occurs. Interventionism fits Koch's postulates in a straightforward way, particularly his emphasis in the third postulate on fully isolating the contagion, growing it in pure culture and showing that when it is appropriately introduced into a healthy animal, the animal exhibits the disease. As discussed in more detail below, isolation of the contagion and growing it in a pure culture are procedures for ensuring that the inoculation has the characteristics of an intervention. Both of these steps are aimed at excluding the possibility that the inoculated material contains confounding factors besides the candidate contagion that might cause the disease. Koch's willingness to conclude that substances not followed by disease after repeated inoculation, do not in fact cause the disease, also fits naturally with the "only if" part of (M).

Interventionism attempts to capture the idea that *experimentation* often has an epistemically privileged role in providing evidence for causal relationships. Here "experimentation" refers to the use of a procedure in which factors or conditions are actually physically manipulated, as when a contagion is isolated through some physical procedure and then injected into an animal's bloodstream. This contrasts with cases where evidence is "purely observational" in the sense that one merely observes patterns of association of factors in nature without physically manipulating those factors. An example involving "purely observational evidence" in the present context would be the observation that bacteria B are always found in animals that exhibit disease D or that whenever bacteria B are present the animal always exhibits disease D, but where there is no experimental manipulation of those bacteria. The limitation of such evidence in establishing causation is that the above observations do not exclude the possibility that some other factor that co-occurs with B is in fact the cause of D. Similar points are expressed by Henle, who stated that a causal proof could not be provided by "direct observation" or "positive observation" of the presence of contagia in cases of disease, since such evidence could not counter the objection that the contagia were mere secondary by-products of the disease "without being the causal material" (Henle 1938; Brock 1999). This same sentiment is expressed by Koch in claiming that his demonstration of an association between tubercle bacilli and the disease, does not respond to the objection that "some other substance" was the cause of the disease (Koch 1987e, 141). From the interventionist perspective, a properly performed experiment can exclude this possibility and it is this idea that is reflected in (M).

In saying that experimentation has a privileged role in establishing causation, we do not mean that one can never reach reliable causal conclusions from observational evidence or that conclusions from experiment are never mistaken. Instead, we mean that when experiments can be carried out they often furnish especially reliable evidence about the presence of causal relationships. In a purely observational context, *if* one knows that C* is or may be a confounder *and* one can detect or measure it, one may be able to correct or control for it via some calculational procedure. However, when there are many potential confounders and many of these are unknown or unmeasured or when one is working with a small sample of cases, it may be difficult or impossible to carry out the needed corrections to reliably eliminate confounders. One of the great

advantages of experimentation is that, in many cases one needs to *know less*, often much less, for the elimination of confounders and reliable causal inference than when the inference is made on the basis of purely observational evidence.

3.2 Structure of the interventionist condition for causation (M). The conditions in (M) have additional structure which is worth underscoring, since they also connect naturally with features of Koch's experimental practice. The first clause (i) in (M) requires that there "exist" a possible intervention on the putative cause C or, more colloquially, that an intervention on C is possible. We will not try to provide a general characterization of what "possible" means here, but instead note the following points. First, since actuality implies possibility, one way of showing that an intervention is possible is to develop a technique for actually carrying out the intervention in question. In the present context this involves developing an experimental procedure for introducing C that is targeted or fine-grained in the sense that it allows one to introduce C into a situation in which C is not previously present, while not introducing other potentially confounding causal agents that might cause disease D. Of course, different candidate causes will require different intervention procedures, since distinct steps must be taken to isolate unique candidate pathogens and remove different types of confounders. It thus makes sense that Koch spends a great deal of time developing such individualized procedures for many of the microorganisms and diseases regarding which he makes causal claims.

Second, (M) requires only that there be "some" possible intervention on C that is associated with changes in D, and not that *all* possible interventions on C have this upshot. Applied to his examples, this means that if Koch is guided by something like (M), to establish causation it is enough that he develop some intervention procedure for introducing the microorganism in an unconfounded way that is reliably associated with the occurrence of the disease. That there may be many *other* experimental procedures for introducing the microorganism into a test animal that are not reliably followed by the disease does not show that the microorganism does not cause the disease, as long as there is at least one such procedure that is followed by the disease. This explains why Koch does *not* conclude, from the failure to produce disease from feeding experiments, or procedures that introduced a pathogen into the digestive tract of an animal, that the pathogen does not cause the disease (Koch 1987a). Thus, it would be a mistake to take Koch to be committed to a version of "causal sufficiency" according to which if C causes D, just any way of introducing C into a test animal must be followed by D. Moreover, it is in our view also a mistake to conclude, that if Koch does not make the inference just described, he must be committed to a "necessary condition" rather a "sufficient condition" conception of causation. Carter relies on inferences of this sort in claiming that Koch did not rely on causal sufficiency in his early anthrax work, arguing that: "[Koch] knew that the mere presence of anthrax bacilli in an animal did not ensure that it would become diseased; ingesting anthrax bacilli did not invariably induce anthrax (1.19), some inoculation procedures were unreliable (i.6), and even among exposed susceptible animals, vulnerability depended on various factors (i.213). So Koch could not claim that the bacilli alone were sufficient to cause anthrax" (Carter 1985; p. 356).

In contrast, we think that Koch (like most researchers) does not hold at any point in this work that if a contagion causes a disease, all inoculation procedures with that contagion will be followed by the disease—contagions should not be expected to be “sufficient conditions” for diseases in this sense. Indeed, finding an intervention procedure that works in the sense of leading to the disease is non-trivial and something that in most cases needs to be discovered empirically on a trial and error basis. For example, Koch discovered empirically that inoculating the ears of mice was unsuccessful in producing anthrax, because the mice were able to “remove the inoculation material by rubbing and licking” their ears (Koch 1987a, 3). He modified his technique by inoculating the mice at the base of their tails, which they could not reach, and found that such inoculations “always have a positive result” in leading to anthrax disease (Koch 1987a, 3). This illustrates that Koch regards it as sufficient to show that there exists an intervention procedure involving the contagion that leads regularly to the disease, even if this is not true for all intervention procedures.

Because what matters is the existence of *some* intervention procedure that is followed by the disease, this has implications (since M provides a necessary, in addition to a sufficient condition for causation) for what would be required to show that a candidate pathogen does *not* cause a disease. To establish this one would need instead to show that there is no possible intervention procedure with the candidate pathogen satisfying the requirements in (M) that regularly leads to the disease. As we will suggest below, Koch does rely on arguments of this form to establish that various candidate pathogens are not causes of a particular disease. For example, Koch claims to have established a conclusion of this sort for non-anthraxic substances in the causation of anthrax—that is, he injects these substances, finds they do not lead to anthrax and concludes on this basis that they are not causes of anthrax (Koch 1987a, 11). As we discuss below, given other assumptions that Koch adopts, establishing negative conclusions of this sort is not as difficult as might initially be supposed.

Note also that the conditional in (M) is a counterfactual: a necessary and sufficient condition for C to cause E is there must be a possible intervention such that *if* it were carried out, a certain consequence would follow. (M) thus does *not* say that for C to cause E an intervention experiment on C must actually be carried out or that the only way we can establish that C causes E is by carrying out such an experiment. This allows for the possibility that it might be feasible to establish that the conditions in (M) are satisfied without actually carrying out an intervention on C. Assuming that Koch adopts an interventionist interpretation of causation, this in turn bears on the question of whether Koch required (or should have required), in order to establish causality, an animal model in which the disease is shown to follow from an appropriate inoculation with the contagion. Our view is that while finding such an animal model is regarded by Koch as a very clear way of establishing causation, he does not regard this as in principle the only way legitimate way of establishing causality. This is consistent with an interventionist framework: if one cannot perform an animal experiment to test for causation and moral considerations rule out experiments on humans, one can sometimes get evidence from other sources about what would happen if the disease were introduced via a suitable intervention without actually performing the intervention in question. One way this might be done is by finding some naturally occurring process that introduces the contagion and has intervention-like features, a so-called natural experiment. This is

essentially what Koch does in the case of cholera, as discussed in more detail in section 6 –he recognized that there was no animal model and yet claimed to have established causality by relying on evidence from cholera outbreaks in certain villages (Koch 1987f).

This last observation connects with another point. An additional role played by (M) is that it can serve as regulative ideal in the following sense: if you want to understand what would be required to show that some factor C causes effect E, think about what would be involved in carrying out a hypothetical experiment in which C is manipulated, and what evidence would show that in such an experiment, E would change. As noted above, the usefulness of this way of thinking is seen in Henle’s description of a hypothetical experiment that, if it were possible to perform, would establish disease causation. This description played an important normative role in suggesting what sort of evidence, in addition to an association between a contagion and a disease is relevant to establishing causation and also may have played a role in leading Koch to devise procedures for actually performing experiments of the sort Henle described.

4 Interventionism and necessary and sufficient conditions. In this section we discuss the relationship between interventionism and other familiar treatments of causation. Many discussions, like Carter’s treatment of Koch’s postulates, connect the notion of causation to the existence of regularities involving necessary and/or sufficient conditions. This is a potent source of confusion because there are many different forms such a connection can take. It will be important for our discussion to distinguish between two of them. The first involves the idea that one can appeal to facts about regularities involving necessary and sufficient conditions to provide a *reductive definition* of causation. (Here “reductive” implies that the regularities associated with causation are characterized in a way that does not presuppose unreduced modal notions like “cause,” “law” etc.) For example, one might claim that “causes” in “C causes E” just means something like “condition C is sufficient for E” (in the sense that there is a regularity such that the occurrence of C is always followed by E), and/or that C is necessary for E (if C does not occur E does not occur), or perhaps that C is both necessary and sufficient for E. A more sophisticated variant of this idea is captured in J.L. Mackie’s well-known view that causes can be defined as INUS conditions (Mackie 1980). On this last view “cause” is understood in terms of complicated combinations of facts about regularities involving necessary and sufficient conditions, more specifically, C causes E if C is a non-redundant (and in this sense “necessary”) conjunct in a condition that is sufficient for E. These are what we called necessary and sufficient condition *conceptions* of causation in section 1.

A second possible view holds that causation cannot be defined in terms of, or reduced to, claims about regularities involving necessary and sufficient conditions, but instead should be characterized in some other way--for example, in terms of (M)¹². However, it is consistent with this view that true causal claims--true, for example, in the sense that they satisfy (M)--may be *associated* with certain regularities, where these regularities may vary, depending on the characteristics of the systems we are trying to understand. On this view there are empirically based constraints involving regularities that pertain to how causes operate in various subject areas, but there is no implication that causes are definable in terms of such regularities and no implication that all causes in all areas of inquiry must operate in terms of these regularities. In our view, much of the discussion of Koch’s postulates in terms of “necessary causes,” or causes understood as

¹² (M) is not reductive because the notion of an intervention is characterized in causal terms.

necessary conditions, versus “sufficient causes,” or causes understood as sufficient conditions, does not distinguish clearly between the two possibilities just described. Koch’s own views about the role of considerations having to do with necessity and sufficiency seem much closer to this second possibility, which for future reference we call the *empirical connection* position.

To take one of the simplest possible illustrations of this second position, suppose, in accordance with Koch’s third postulate, that: (K) a type of bacterium B can be isolated and that when it is properly injected into an animal host, a particular disease D always occurs. Suppose one regards the satisfaction of condition (K) as sufficient to establish that infection with B causes D. “Sufficiency” is involved in condition (K) in at least two ways: (4.1) first, fulfillment of (K) is taken to be *sufficient in establishing* that B causes D and (4.2) second, condition (K) requires that cause B itself be a *sufficient cause* in the sense that the proper introduction of B into the animal always leads to or is in the context “sufficient for” D. Note, however, that condition (K) does *not* in itself imply that (4.3) if some factor X is always followed by Y (that is, X and Y are correlated, but it has not been shown that interventions on X are followed by Y), it follows that X is a cause of Y, which is what a definition or conception of cause in terms of a regularity involving a sufficient condition implies. This holds even if X is a microorganism that when found in an animal is always followed by disease Y. Not only does (4.3) does not follow from condition K, but (4.3) is clearly methodologically objectionable because, as observed above, it is insensitive to considerations regarding confounding. More generally (and for parallel reasons) there are compelling normative objections to any version of the idea that “cause” can be defined in terms of claims about the obtaining of regularities involving necessary and/or sufficient conditions: all such views fail to distinguish between causation and correlation. Of course it does not follow just from the normative inadequacy of conceptions of causations framed in terms of regularities involving necessary and sufficient conditions that Koch did not hold such a conception. Nonetheless given Koch’s evident concern with ruling out confounding and the importance he attaches to intervention experiments, it would be surprising if he held a conception of causation which does not fit with this concern and which fails to distinguish causation and correlation. Supposing Koch to be committed to an interventionist conception of causation makes much better sense of his reasoning and experimental procedures.

5 The status of Koch’s first and second postulates. In this section we provide an analysis of Koch’s first and second postulates in terms of *causal specificity* assumptions, which we understand as empirical connection claims of the sort described in Section 4. We first describe these assumptions and then discuss their role in Koch’s causal reasoning.

5.1 Causal specificity assumptions. If it is correct that Koch does not hold a conception according to which causation is just a matter of regularities involving necessary and sufficient conditions, what should we make of Koch’s first and second postulates? Recall that these say, respectively that:

1. The contagion occurs in every case of the disease.
2. The contagion does not occur in other diseases or non-pathogenically.

Beginning with the first postulate, rather than taking it to involve a commitment to the claim that causation itself can be characterized in terms of the presence of a regularity in which the cause is a necessary condition for its effect, we suggest instead that it rests on an empirical claim about a kind

of specificity that we should expect in the causation of certain diseases, where the operative notion of cause is the interventionist one. In particular, the first postulate rests on something like the following *specificity of cause* assumption:

- (5.1) *If a pathogen of type C is a cause of a disease of type D, according to the interventionist account of cause as described in (M), then the following claim will hold as a matter of empirical fact: causes of type C are the only pathogens that cause diseases of type D.*

Obviously if assumption (5.1) is correct, then it is sensible to adopt Koch's first postulate: to count as a cause of a disease, evidence must be provided that the pathogen is present in every case of the disease. The second postulate, on the other hand, can be understood as resting on the following *specificity of effect* assumption:

- (5.2) *If a pathogen of type C is a cause of a disease of type D, according to the interventionist account of cause as described in (M), then the following claim will hold as a matter of empirical fact: C's do not cause any other disease of a different type D.*

Again, if assumption (5.2) holds, it makes sense to adopt Koch's second postulate. Both (5.1) and (5.2) are claims about what is often called *causal specificity*: that a given type of effect can only have one type of cause (specificity of cause) and/or that a given type of cause can only have one type of effect (specificity of effect).¹³ On this construal of Koch's postulates, neither of these specificity claims follow from the notion of causation itself--they are not built into some definition of causation that Koch adopts. This is as it should be: on any plausible conception of cause, including interventionism, it is possible both that an effect might have many causes and that a cause might have many different effects. We thus agree with the many commentators who argue for this point in connection with Koch's postulates. However, we take Koch to be supposing that, although it is not part of the definition of cause that either causes or effects must be specific, it is also true, as a contingent empirical matter, that the specificity claims (5.1) and (5.2) hold for most or all of the particular diseases he investigates, even if they do not hold for all causes or even for all diseases. Of course, Koch is *right* that such assumptions hold for anthrax, cholera, tuberculosis and other common infectious diseases. Furthermore, given the historical context surrounding Koch's work, it makes sense that he would rely on such causal specificity assumptions. Koch's work provided crucial evidence for their being uniquely distinct bacterial species and his attention to single species in his research led him to identify diseases that well fit a mono-causal model and could be well classified as caused by a single type of bacteria. This approach resulted in a sort of "mutual definition," where diseases were defined through their bacterial contagions, and the contagions were often named for the disease they produced (Gradmann 2009, 84; Mazumdar 1995, 66, 68). Koch viewed this method as providing a decisive standard for "specifying the boundaries" of some diseases, which had been unattainable with previous studies of disease causation.¹⁴ For these

¹³ For more discussion of causal specificity, see (Woodward 2010).

¹⁴ For example, when Koch established that the tubercle bacilli caused tuberculosis, many previously distinct disease categories--military tuberculosis, caseous pneumonia, caseous

reasons, Koch's is often viewed as committed to a strict "one-to-one monomorphic relationship of the disease and its [bacterial] organism" (Mazumdar 1995, 75). Koch's reliance on causal specificity assumptions also led him to focus on disease examples that provided the strongest argument against transformationist theories and that could be straightforwardly supported with experimental evidence at a time when significant skepticism surrounded contagionist views.

As we illustrate below, the relevance of these causal specificity claims to Koch's reasoning is that *if* they are true or reasonable to assume, then they make the problem of identifying pathogenic causes of various diseases much easier than it would otherwise be. To put the role of these assumptions in modern terms, they limit the space of alternative hypotheses about disease causation within which he needs to search and thus facilitate identification of the correct hypothesis. To spell this out, we need to further clarify the specificity claims themselves. First, note that as we have interpreted them, both claims are relativized or restricted to more general categories in which the types of causes and effects fall. For example, (5.1) does not claim that diseases have only one type of cause *simpliciter* but rather that, within the general category of pathogens, each disease will have only one type of pathogen as its cause. Thus, (5.1) is consistent with the disease also having causes that are not pathogens—for example, occurrence of the disease might also be influenced by the state of the subject's immune system. This is a reflection of the fact that Koch is searching among *pathogens or contagions* for the causes of various diseases, not trying to discover all possible causal factors influencing those diseases. Obviously this more restricted claim is much more likely to be true, at least for certain diseases, than the unrestricted claim. Similarly, (5.2) does not claim that each type of pathogen has only one type of effect, which would be absurd, but rather that it causes only one type of disease, rather than several different types of diseases.

Carter (1985, p. 360) and other commentators such as Broadbent (2009, 303-4) and Kelly (2001, 21; 2007, 95) attempt to interpret Koch's second postulate as a sufficiency claim of some kind. We think this is because they understand Koch to be working with a conception of causation that is characterized in terms of necessary and sufficient conditions, and since the second postulate is obviously not a necessity claim, it looks to them as though the only alternative is to interpret it as a sufficiency claim. However, the second postulate is not a sufficiency claim in any obvious sense—there is nothing in the notion of a cause being sufficient for an effect that implies that it can have only one kind of effect. In particular, if the claim that a pathogen is causally sufficient for some disease means simply that the occurrence of the pathogen is regularly followed by the disease, which is the notion of sufficiency that seems to be assumed, there is no reason why a given type of pathogen cannot be causally sufficient for many different diseases, in contravention of the second postulate. Our interpretation of the second postulate as the assumption that a cause can only have one type of effect of some more general kind, as indicated in (5.2), says something very different from the claim that this cause is sufficient for its effect.

Similarly, these authors interpret the first postulate as a necessity claim, which can be characterized as the claim that (5.3) a regularity holds that specifies that whenever disease D

bronchitis, and others—were merged into one disease category once it was realized that they were all caused by the same tubercle bacilli (Koch 1987d, 93). This is an instance of a more general strategy of re-defining cause and effect variables in such a way that they come closer to satisfying one-cause, one-effect requirements of specificity.

occurs, factor C is present. However, notice that this claim (5.3) is compatible with its also being true that a regularity holds that specifies that whenever D occurs, pathogen C*, which is different from C, is also present. In other words, an effect can have more than one “necessary condition,” in the sense of a condition that must be present if the effect is. Our interpretation of Koch’s first postulate as claim (5.1), rules out this possibility in the case of disease causation. Thus, saying that a type of cause is necessary for a type of effect in the regularity based sense under discussion is quite different from saying that that type of cause is the only cause (within some more general category for that type or effect), which is what claim (5.1) says. For these reasons among others, the construal of the first two postulates in terms of regularities involving necessary and sufficient conditions does not do a good job of capturing their content or how they are used in Koch’s reasoning.

5.2 The role of Koch’s first and second postulates in his reasoning.

The appeal of specificity assumptions like (5.1) and (5.2) is that when true they can be used to support and facilitate various inductive inferences about disease causation and that they limit the space of alternatives among which the investigator must chose. Here are some illustrations. Suppose it is true, in accord with (5.1), that if some pathogen C causes disease D, then C is the only cause of D. Then, given a candidate cause, C* for D and the further plausible assumption that every disease has at least one cause, one can exclude the possibility that C* causes D just by finding some cases in which D occurs without C*, since such cases show that D must have some other cause distinct from C* and hence by (5.1) that no cases of D can be caused by C*. (As we note below, this seems to capture at least part of Koch’s reasoning in his anthrax papers.) Suppose, by way of contrast, that disease D can have lots of different causes. Then if one fails to find that C* is present in some cases in which D occurs, this does not exclude the possibility that C* causes D in other cases. Thus if it is possible that D has many causes, ruling out candidate causes as genuine causes of D is much more difficult than it would be if, in accord with Koch’s first postulate, D can have just one cause.

Of course it is true that merely ruling out candidate causes for D does not by itself establish what does cause D. Moreover, as noted above, even if one if one finds some candidate cause C which is present whenever D occurs, this does not establish conclusively that C causes D, since there may be some other factor K which is also present whenever D occurs and which in fact causes D. This is why, normatively speaking, doing an intervention experiment in which one isolates C is so important. On the other hand, because Koch’s first postulate can be used to eliminate many alternative candidates for the cause of D, it certainly is very helpful in restricting the space of alternative possibilities among which one needs to search in looking for the cause of D. As argued above, given the first postulate, there is, strictly speaking, no need to do intervention experiments on some candidate cause C* as long as one has observed cases in which D occurs without C*. (Of course one might want to do such an experiment anyway, since a negative result for a range of attempted intervention procedures would provide additional support for the conclusion, in accord with the only if part of (M), that C* does not cause D.) We may also add that even though finding that some factor C is present whenever D occurs does not by itself show that C causes D, it does, within Koch’s framework, imply the following: That either C causes D or else C is always associated

with something-like K above—that causes D. This consideration also can facilitate identification of K, since one now knows to look for it in those contexts in which C also occurs.

Turning next to Koch's second postulate, it also plays a role in substantially restricting the space of alternative hypotheses among which one needs to search in finding the cause of a disease. Suppose one is interested in disease D. If one can establish (e.g. by means of an intervention experiment) that some candidate pathogen C* causes some disease D* distinct from D, then, in accord with the second postulate, one can rule out the possibility that C* also causes D, thus allowing attention to focus on the remaining possible candidates for the cause of D.

Note also that both the first and second postulates also help considerably with issues having to do with confounding. A confounder for some candidate cause C is some other factor C* which is a potential cause for D. If one can either find some case in which D occurs without C* or some case in which C* causes some disease D* distinct from D, one can infer (in accord with Koch's first and second postulates, respectively), that C* is not a cause of D. Thus even if C* is present in the investigative context, one does not have to worry about its being a confounder for C.

These observations bear on another set of issues concerning Koch's postulates. Modern commentators note that postulates are useful for some diseases (as evidenced by Koch's discoveries) but of limited usefulness for others: Koch's criteria serve as an important guide to identifying causal relationships in biomedicine, but also have a number of serious limitations and are unable to account for the causal etiologies of many medically recognized diseases. Our treatment of the postulates makes sense of both of these features. As contingent empirical assumptions about disease causation, the postulates hold for certain diseases and not others. Koch focused on a set of diseases for which these assumptions held and exploited this fact in the inferences he made. This is consistent with there also being many diseases for which these assumptions fail. By contrast, if the postulates are interpreted as describing features that are built into meaning of the concept of causation adopted by Koch, then it becomes much more puzzling how the postulates can be both useful and not universal.

6 Some Additional Aspects of Koch's Reasoning. With these observations in mind let us look at some additional details of Koch's reasoning. As we noted above, Carter claims that early in his work on anthrax Koch adopted a necessary condition criterion and/or conception of causation, only later shifting to a necessary and sufficient condition conception (Carter 1985; Carter 1987a). In contrast, we interpret Koch as making use of all three of his postulates and as holding an interventionist conception of cause throughout his work. In this section, we discuss features of Koch's method of establishing causality throughout his early publications on anthrax, mid-career papers on tuberculosis, and later work on cholera.

6.1 Anthrax (1876, 1881, 1882). Koch begins his 1876 paper with references to work by Casimir Davaine, a French physician who used inoculation experiments in studying anthrax and the small "rods" identified the blood of anthracic animals. Koch states that in Davine's research with "*numerous inoculation tests with fresh or dried blood containing these rods*, he asserted that the rods were bacteria and that the disease could occur only when these rods from anthrax blood were present" (Koch 1987a, 2; emphasis added). Koch mentions Davine's work, because although it was considered the best evidence that anthrax bacilli caused anthrax, Davine's claims had been

“contradicted from several sides” (Koch 1987a, 1). Davine could not account for two serious objections: (6.1.1) why the disease was often transmitted in barren, insect-free pastures that were presumably hostile to living contagions and (6.1.2) how anthrax was produced in animals inoculated with bacilli-free blood. These shortcomings led many scientists to deny that the bacteria were causally implicated in anthrax or that they were “significant” for the disease in any way (Koch 1987a).

Koch addressed the first objection by demonstrating that the anthrax bacilli gave rise to resistant spores that could withstand harsh environmental conditions without requiring an animal vector.¹⁵ He demonstrated that, after surviving such conditions, the spores could produce viable anthrax bacilli. The identification of anthrax spores also allowed Koch to respond to the second objection. The fact that prior researchers found animal inoculation experiments with bacilli-free blood to produce anthrax could be explained by the fact that such inoculations were contaminated by unidentified anthrax spores. The unidentified spores produced anthrax bacilli which ultimately caused the disease. Koch conducted numerous inoculation experiments with anthrax spores and bacilli to substantiate this claim and to “prove” that these anthracic substances caused the anthrax disease. The following passage from Koch’s paper reveals important features of his experiments and argument for causation:

It has been claimed that the disease caused by inoculation with anthrax blood is identical with septicemia. This claim could be taken as an objection to my inoculations with decaying anthrax substances. To refute this objection, I frequently inoculated mice with decaying blood from healthy animals and with decaying aqueous humor and vitreous humor that was free from bacilli. These animals nearly always remained healthy. Moreover, I also inoculated animals with decaying vitreous humor in which a species of bacillus had spontaneously developed that was very similar to *Bacillus anthracis*. The spores of the two species could not be distinguished by size or appearance, but the filaments of the vitreous humor bacilli were shorter and more clearly articulated. In spite of numerous attempts, my inoculations with these bacilli and with their spores never caused anthrax. Animals also remained healthy after inoculation with spores of hay-infusion bacilli cultured by Professor Cohn. *On the other hand, I often inoculated with spores masses that had been cultured in vitreous humor and that, as I had convinced myself by microscopic examination, were derived from entirely pure cultures of Bacillus anthracis. The inoculated animals invariably died of anthrax. It follows that only one species of bacilli can generate this specific disease.* Other inoculated schizophytes are either harmless or cause a completely different disease process. ... *This last experiment is sufficient proof that spores of Bacillus anthracis cause anthrax when introduced directly into body fluids* (Koch 1987a, 12; emphasis added).

Carter claims that this and other passages indicate that Koch was primarily interested in establishing that the bacilli were necessary for anthrax, and that Koch himself states his argument

¹⁵ Koch’s elucidation of the spore-forming life cycle of *Bacillus anthracis* significantly influenced the advancement of bacteriology through the development of important techniques, (e.g. hanging-drop method, pure culture and sterile techniques) and support for the fixed species conception of microorganisms.

in this way. Carter notes that Koch attempted to generate anthrax by inoculating hay-infusion bacilli, anthracic materials without bacilli, and look-alike non-anthrax bacilli. However, Carter claims that since these inoculations failed to produce anthrax, Koch concluded that anthrax could only be produced if bacilli or spores were present. In discussing Koch's successful inoculations with anthracic material, Carter claims that "Koch infers that bacilli cause anthrax from the observation that anthrax occurs only if injected substances contain bacilli or spores. Thus, he is presupposing necessity as the criterion for identifying the cause of anthrax. Here, and in other passages, Koch clearly regards necessity as decisive in establishing causality" (Carter 1985). Carter also understands Davaine's argument, as "an argument for causal necessity," because he claimed to always find the bacilli in the blood of anthracic animals and that bacilli-free inoculations never produced the disease (Carter 1985, 355).

The italicized passages make it clear that Davaine performed inoculation experiments in which rods associated with anthrax disease were injected into test animals, and that Koch performed such experiments in which isolated anthrax bacilli and spores were injected into the blood systems of test animals, and that in both cases these animals died of anthrax. Koch's discussion of his own work in this paper is clearly a description of an intervention experiment in which he takes himself to have established that anthrax spores cause anthrax, not just by observing that they are necessary for anthrax, but by demonstrating that appropriately introducing them is always or "invariably" followed by anthrax. However, instead of inoculating whole blood contaminated with anthracic materials as Davaine and prior researchers had done, Koch inoculated "pure cultures" of anthrax bacilli and spores. This allowed him to attribute the ensuing anthrax disease to these anthracic materials, as opposed to other candidate causes that might be injected with the whole blood. He explicitly states that these inoculation experiments, which always result in the disease, provide "sufficient proof" that the anthrax spores cause the disease. Here he seems to be reasoning in accord with the sufficiency clause of (M) and his third postulate.

It is also true, as the quotations above make clear, that Koch attaches a great deal of importance to the fact that the injection of other kinds of bacilli and non-anthraxic substances associated with anthrax, do not lead to the disease. However, it seems to us that the most natural way of interpreting these passages is that they reflect a concern with isolating the cause of anthrax and ruling out potential confounding factors—that is, Koch is concerned to ensure that the introduction of the spores and bacilli meets the conditions for an intervention. For example, one possibility is that some substance in the blood or tissues of anthracic animals, other than the anthrax bacilli or spores, might be the true cause of the disease with the bacillus and spores just being accidental concomitants or confounding factors. Showing that inoculations with these non-anthraxic substances do not lead to the disease rules out this possibility in accord with the necessity clause of (M). Similarly, showing that inoculations (with various inoculation procedures) with non-anthraxic bacilli do not produce the disease rules out the possibility that they cause anthrax, which also increases the plausibility of the claim that some other bacterium must be the cause, via a sort of eliminative argument. The observation that injection of various other bacteria, when not harmless, causes some other disease also supports the conclusion that these other bacteria cannot also be causes of anthrax via Koch's second postulate that claims that each specific type of bacterium causes a specific disease, so that if a bacterium causes a disease distinct from anthrax it cannot also cause anthrax.

6.2 Tuberculosis (1882, 1883, 1884). When Koch began his work on tuberculosis it was the leading cause of death among all age groups¹⁶ and, despite painstaking efforts, ongoing research was unable to identify its causal etiology. Koch's research provided the first identification of the tubercle bacilli (*Mycobacterium tuberculosis*) and established its causal relationship to tuberculosis, research that would win him the 1905 Nobel Prize in Physiology or Medicine. In his publications on tuberculosis Koch claims to rely on the same procedure he used to clarify the etiology of anthrax. In re-describing his anthrax work to illustrate this procedure, he writes: "This procedure, which proved the parasitic nature of anthrax, and the consequences that necessarily followed from results obtained in this way were the basis for my investigations of the etiology of tuberculosis. Thus, these investigations involved, first, demonstrating the pathogenic organisms, then isolating them, and finally reinoculating them" (Koch 1987e, 132). Koch's investigation into the etiology of tuberculosis was facilitated by his use of a new staining technique that allowed him to identify a previously unknown bacterium that was regularly associated with tuberculosis. He discusses how this association was an important first step in this procedure, but that this alone was unable to establish causation, which required the use of inoculation experiments. After describing specific features of the tubercle bacilli and their regular presence in tuberculous processes, Koch further clarifies his method of establishing causation:

Up to this point, I have proved that tubercle bacilli are present in *all tuberculous processes and only in such processes*. I have also shown that only substances containing tubercle bacilli can generate tuberculosis. However, in both cases the bacilli were *associated* with other body constituents. *One could still suspect that some other substance was the actual infectious material, and that the bacilli played only a secondary role. This question can only be decided by inoculating pure bacilli. They must be separated from all other body constituents. If they still cause tuberculosis, they are the single and unquestionable infection material.* The great significance of precisely this part of the investigation requires the strictest measure to preclude all errors (Koch 1987e, 141; emphasis added).

In his first paper on tuberculosis, Koch describes his results from thirteen different inoculation experiments with around 10 different species of animals and varying tuberculosis sources. In each experiment he inoculated a subset of the animals with pure cultures of tuberculous materials, while the other animals served as controls, either uninoculated or inoculated with material other than tubercle bacilli. In order to ensure that the tubercle bacilli were in pure culture and completely separated from all other body constituents, Koch grew the bacilli in simple artificial media for extended periods of time (in one experiment, up to 113 days), with constant transfers to fresh media. As he states:

"In these experiments, many animals received the bacilli in different ways—through simple inoculation in the subcutaneous tissues, through injection into the abdominal cavity, into the anterior chamber of the eye, or directly into the blood stream. Without exception, they all became tuberculous. Not only were nodules formed, but the number of tubercles was in proportion to the number of bacilli introduced...Second, the control

¹⁶ <http://www.britannica.com/EBchecked/topic/608235/tuberculosis-TB> (britannica)

animals remained healthy; they were treated exactly like the infected animals, the only difference was that they received no bacilli. Third, for other purposes, numerous guinea pigs and rabbits were also inoculated and injected with other substances. Typical military tuberculosis never occurred among them. This can happen only when the body is suddenly overwhelmed by a large number of infecting germs. All these facts, taken together, show that the bacilli in tuberculous substances are not merely coincidental with tuberculosis, but cause it. These bacilli are the real tuberculosis virus" (Koch 1987d, 93).

As seen in these passages, Koch's method of establishing the causal etiology of tuberculosis follows the methodology of his anthrax experiments, just as he claims. His first and second postulates are captured by the initial steps of identifying a "characteristic" bacterium that is associated with all cases of a particular disease, and only this particular disease. We view these steps as relying on the assumptions of causal specificity, as outlined in section 5. If these assumptions are correct, (at least for some diseases) then identifying one-to-one associations between a specific contagion and disease provide a tractable and reliable place to look for causal relationships. Koch clearly views evidence of such associations as identifying promising candidates for causal relationships, but as unable establish causation alone. Koch does not view the simultaneous occurrence of the bacteria and disease, or even the fact that the disease can only be produced by inoculation with material containing the bacilli (and other potential causes), as establishing causation, because such information cannot rule out alternative causes, or confounders, that are also present with the tubercle bacilli.

Koch states that determining whether the bacilli and disease stand in a causal relation "can only be decided by inoculating pure bacilli," which is the final step of his procedure. Koch conducts this final step with 13 animal inoculation experiments, where he demonstrates that inoculation with pure cultures of tubercle bacilli always produces tuberculosis, while control animals remain disease-free. Koch's experiments are paradigmatic interventionist experiments: they involve an unconfounded manipulation of the candidate bacterial cause, to establish its relation to the disease effect of interest. Koch ensures this with the extreme measures he takes to completely isolate the tubercle bacilli, so that only they are inoculated into animals, and so that control animals are treated exactly the same where the "only difference was that they received no bacilli" (Koch 1987d, 93). An interventionist interpretation captures Koch's emphasis on the significance of his inoculation experiments, because they clarify how such experiments distinguish between mere association and causation. It is unclear why Koch would place so much importance on such a sophisticated experimental procedure, or include animal experiments at all, if he maintained a conception of causation according to which it is just a matter of regularities involving necessary and sufficient conditions, which can be identified by observation alone.

6.3 Cholera (1884, 1884) Koch's publications on cholera provide insight into the role of animal inoculation experiments in his method of establishing causality. This is, in part, due to the fact that there was no available animal model for cholera at the time of his research. Similarly, to his prior work, Koch begins his 1884 cholera paper by describing the identification of a particular bacteria, in this case the "comma bacilli," that he states are found in all cases of cholera and only in such cases (Koch 1987f, 157, 159). In discussing how to clarify the relationship between the bacteria and

disease, Koch states that “[t]he only possibility of providing a direct proof that comma bacilli cause cholera is by animal experiments” and that “[o]ne should show that cholera can be generated experimentally by comma bacilli,” statements that reflect his third postulate (Koch 1987f, 160). However, after failed attempts to infect various types of animals (including monkeys, cats, chickens, dogs, etc.) with the bacteria, Koch concludes that animal experiments cannot yet be provided, as “all the animals available for experimentation and those that often come into contact with people are totally immune” (Koch 1987f, 161).

From these findings, Koch decides that “we must dispense with this part of the proof,”¹⁷ but that “[t]his certainly does not mean that there is no proof that comma bacilli are pathogenic” (Koch 1987f, 161). Koch provides two reasons supporting the claim that comma bacilli cause cholera. First, he claims that an “argument by analogy is fully justified here,” because recent evidence has definitely established that some infectious diseases have bacterial causes, and it is reasonable to assume that cholera is just like these diseases. He also mentions diseases like leprosy that were understood to be bacterial in origin, but that also lacked animal models, indicating that the lack of an animal model did not commit one to denying a bacterial etiology. Second, Koch supports the bacterial etiology of cholera by appealing to natural experiments in the human population. (For our purposes, a natural experiment involves the natural, unplanned occurrence of an intervention-like process that introduces or removes a candidate cause.) He describes cholera outbreaks that are traced to large amounts of comma bacilli, “usually in a nearly pure culture,” in the laundry of those infected with cholera, where these cholera outbreaks can be “can be conceived as experiments conducted under natural conditions” (Koch 1987f, 161-162). These outbreaks include a community-wide cholera epidemic after a cholera victim washed laundry in the shared water supply and the high incidence of the disease among laundry personnel. Since these cholera samples are close to being a pure culture, Koch claims that “if an infection comes about through cholera laundry, it can only have happened because of these organisms. Suppose that laundry personnel become ill after eating with contaminated hands or that they are sprayed with laundry water that contains the bacilli and that a few drops reach their lips. These conditions simulate an experiment in which small quantities of pure cultures are fed to humans. These persons unknowingly perform experiments, on themselves and the experiments are as conclusive as if they have been intentional. Moreover, these observations are so common and have been made by so many different physicians that there can be no doubt about their reliability” (Koch 1987f, 161-2). Koch claims that these natural experiments are “as conclusive as experiments on humans” and that they establish that the comma bacilli cause cholera (Koch 1987f, 161).

Some have argued that in his cholera publications Koch relies on yet another distinct set of causal criteria that differ from the criteria he employs in his earlier work (Carter 1985). It is suggested that Koch perhaps omits his third postulate from his causal criteria in the case of cholera, realizing that it cannot be fulfilled in cases where animal models are unavailable. However, the claim that he revised his postulates in this manner is undermined by the fact that he continues to emphasize the role of animal inoculation experiments in his cholera papers, in other papers published in the same year, and also in his later work (Koch 1987g). Rather than reading Koch as completely eliminating his third postulate in his cholera publications, we understand him as claiming that in cases in which no animal model is available other forms of evidence can provide

¹⁷ Another translation of this is “We must, therefore, waive this evidence” (Koch 1884, 37).

evidence for a causal relationship. These claims support our view that Koch regarded animal inoculation experiments as a reliable method of establishing causality, without regarding them as the only method capable of establishing causality.

7. Conclusion: Koch's postulates throughout his work. We have argued that Koch's postulates are best understood within an interventionist account of causation. Koch claims that to establish that a contagion is the cause of a particular disease involves providing evidence that inoculating the contagion, and only the contagion, into a laboratory animal would reliably produce the disease in question. We have suggested that these inoculation experiments are straightforwardly understood within an interventionist framework: they establish the existence of a causal relationship by showing that the unconfounded experimental manipulation of the candidate cause is followed by the effect of interest. The role Koch assigns to these experiments makes sense given their ability to distinguish causal relationships from mere correlations, and the fact that identifying methods that could reliably make this distinction was one of the dominant interests and concerns of his research community.

Our interpretation of Koch's postulates treats them as a fairly consistent method that he relies on throughout his work. We view this as an advantage of our account, because it is supported by Koch's discussions of his own work. Koch claims that he relies on the same method throughout his work and that he first introduced this method in his earliest anthrax publications (Koch 1987e, 132). It is true that Koch's tuberculosis papers contain some of his most explicit descriptions of his causal criteria. This presumably explains why many scholars claim that Koch's postulates first appear in his tuberculosis publications¹⁸. However, while Koch's tuberculosis publications are important for various reasons, we do not view them as containing the first discussion of his causal criteria.

In addition, our analysis interprets Koch's first two postulates as involving causal specificity assumptions. These assumptions apply to particular diseases that have a single main causal factor (specificity of cause) and where this factor is capable of producing a single disease (specificity of effect). With respect to modern biomedicine, it is clear that these assumptions are not universally applicable to all human diseases. However, they do hold for nearly all of the diseases that Koch and his contemporaries examined. For the diseases and causal factors that meet these specificity assumptions, Koch's postulates are an incredibly powerful method of establishing causation. At a time when many scientists fervently denied that microorganisms could cause disease, this method was instrumental in substantiating germ theory and reshaping mainstream views on disease causation. Appreciating how this historical context influenced Koch's criteria and understanding the assumptions that they depend on, clarifies how Koch's postulates provide a useful, yet not universal, criteria of disease causation.

Finally, we think that our interpretation of Koch illustrates a way in which an improved

¹⁸ Another potential reason for this is that Koch's research on tuberculosis has received significant attention due to its relevance for controlling a common human disease, and this attention may encourage a tendency to view his tuberculosis work as importantly distinct from his prior research.

philosophical treatment of causation can lead to an enhanced understanding of various aspects of experimental practice in science. Features of Koch's experimental practice that previously were not well understood can be illuminated by viewing them through the lens of an interventionist account of causation. We believe that this account provides resources for the reconstruction of other important episodes in experimental science, but this is a topic for another paper.

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