“To Rid Oneself of the Uninvited Guest”: Robert Koch, Sergei Winogradsky and Competing Styles of Practice in Medical Microbiology

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Abstract Does an infectious disease have one, singular pathogenic cause, or many interacting causes? In the discipline of medical microbiology, there is no definitive *theoretical* answer to this question: there, the conditions of aetiological possibility exist in a curious tension. Ever since the late 19th century, the “germ theory of disease” – “one disease, one cause” – has co-existed with a much less well known theory of “multifactorality” – “one disease, many interacting causes”. And yet, in *practice*, it is always a singular and never a multifactorial aetiology that emerges once the pathogenic world is brought into the field of medical perception. This paper seeks to understand why. Performing a detailed, genealogical reading of the 2003 severe acute respiratory syndrome (SARS) outbreak, it foregrounds a set of links that connect the practical diagnostic tools at work within contemporary, 21st century laboratories to the philosophical assumptions at work within late-19th century understandings of the “germ theory of disease”.

Does an infectious disease have one, singular pathogenic cause or many, interacting causes? In the medical microbiological sciences, there is no definitive answer, one way or another, to this question: there, the conditions of aetiological possibility exist in a curious tension. Ever since the birth of the “germ theory of disease” and the concomitant birth of the singular aetiological object, these conditions have allowed for the co-existence of a very different, and far less well understood kind of object: the multifactorial object. And yet, despite the fact that practitioners consider both answers to be plausible and possible, ours is a world defined almost entirely by the “germ theory of disease”. Acquired immunodeficiency syndrome (AIDS), caused by the singular human immunodeficiency virus (HIV); severe acute respiratory syndrome (SARS), caused by the singular coronavirus (CoV); hemophagocytic syndrome (HPS) caused by the singular Epstein-Barr virus, and so on and so forth: whenever the pathogenic world is brought into the field of medical perception it is almost always the singular,

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and never the interactive microbe, that we see. So how did we get here – to a world in which microbes could be understood in this, the most singular of ways? Because out there, in the pathogenic world, things really are singular? Because the possibility of the multifactorial disease has very rarely existed as anything other than a theoretical possibility? Pursuing a genealogical-historical case-study of the 2003 SARS-CoV outbreak, this paper suggests not, or at least not *quite*, to both of these suggestions.

The paper is divided into six sections. The first section seeks to make clear the historical recurrence of this tension between singular and multifactorial understandings of disease aetiology within the field of medical microbiology. The second section introduces the case-study, foregrounding a particular moment during the SARS outbreak at which the possibility of a multifactorial aetiology flashed up precisely as a possibility, before being extinguished by advocates of the germ theory of disease. Setting the scene for the analytical sections to follow, it makes clear that the diagnostic technology of the pure cell-culture was crucial to this act of extinguishing. The third section seeks to develop an understanding of why, and how, the cell-culture was able to act in this way. To do so, it traces a path back to the late 19th century, and a controversy that flared between two scientists with very different understandings of aetiology: on the side of singularity, the German bacteriologist Robert Koch, and on the side of multifactoriality, the Russian microbiologist Sergei Winogradsky. What becomes apparent is that practitioners on either side of this controversy developed practical, methodological tools that were able to vindicate empirically their own theoretical understandings of the microbial world: on one side, methods of culturing microbes that allowed for the possibility of singular aetiologies to emerge; and, on the other side, methods that allowed for the possibility of multifactorial aetiologies to emerge. Armed with this knowledge, the fourth section of the paper returns to the SARS outbreak in order to study the cell-culture, the diagnostic technique upon which medical microbiologists were entirely dependent during their attempts to isolate aetiological agents from patient samples. Developing a deep, textual reading of this technique it is suggested that the 21st century cell-culture remains epistemologically rooted on one side of the methodological divide that emerged during the founding 19th century controversy – in a similar manner to Robert Koch's original culture method it was allowing for the production of a singular pathogen whilst also, and at the same time, suppressing any possibility that an interactive assemblage of pathogens might emerge from patient samples. Thinking through the work of the philosopher Ian Hacking, the fifth section suggests that the methodological tools currently involved in

the practice of medical microbiology index a particular “style of practice” in which it is, at present, easier to ignore the empirical possibility of multifactoriality than to try and recover it. But what of the stability of that “present”? Posing this question, the final section of the paper reflects on recent, tentative modifications to the technique of cell-culturing which appear to be making it easier to coax theoretical multifactoriality out into a space of empirical visibility. The paper concludes with a discussion of what this movement towards revisiting and readopting techniques and principles of culturing first advocated by Sergei Winogradsky during the 19th century might mean for our 21st century understandings of the concept “infectious disease”.

The Singular and the Multifactorial

Written by the French microbiologist René Dubos, *Mirage of Health: Utopias, Progress, and Biological Change* was first published in 1959.¹ Ostensibly an introduction to the idea of medicine as a social science, Dubos used *Mirage of Health* to develop what can best be described as a general philosophy of life. In one chapter therein, “Environment and Disease”, he pauses to ask the following question: is the doctrine of specific aetiology, in which one disease is held to have one cause, still a useful aid for studies of disease causation in humans?² Initially he appears to be suggesting that yes, it is. “Unquestionably” he writes, “the doctrine of specific aetiology had been the most constructive force in medical research for almost a century”.³ It had achieved “spectacular successes and gained almost universal acceptance in medicine”.⁴ Indeed, the “theoretical and practical achievements to which it has led [now] constitute the bulk of modern medicine”. “Louis Pasteur, Robert Koch, and their followers” had “shown by laboratory experiments that disease could be produced at will by the mere artifice of introducing a single specific factor – a virulent microorganism – into a healthy animal”.⁵ Such comments would not have seemed at all out of place in 1959. For western medical practitioners like Dubos, the 1950s and 1960s were a time of great optimism. The doctrine’s “spectacular successes”, its previous “practical and theoretical achievements”, had created a climate in which it was by no means impossible to dream of a time, perhaps a time not too far distant, when all but the most insignificant of infectious diseases would have been conquered. Dr. Salk’s mass experimental polio vaccinations, stretching from 1955 to 1967, not only made the might of modern biomedicine witnessable to all during this period – reducing cases in America, year by year, from 76,000 to 1,000 – but also served to strengthen, to make plausible, those medical dreams.⁶

Indeed by 1967 the U.S. Surgeon General, William H. Stewart, would be so convinced of imminent success in the fight against infectious diseases, that he would tell a White House gathering of state and territorial health officers it was time to “close the book” on infectious disease research.⁷ All national attention was now to be re-directed towards understanding what he termed “the new dimensions of health”: chronic diseases.⁸

But Dubos was no optimist. The closure envisaged by Stewart was for him little more than a mirage. Whether knowingly or not, Dubos suggested, those who believed such a closure to be at all possible were in thrall to an Aristotelian philosophy of life.⁹ There, “the affairs of man [sic] and the external environment” were held to be separable, with any interplay between the two controllable, in the final instance, by “man”.¹⁰ For Dubos, this was hubris. The interplay was not so much pure and controllable as processual and unpredictable. In life Dubos saw only impurity; a co-implication of human, bacterial and viral existence; a mutual immersion in the conditions of each other’s evolution. If Stewart’s book *had* existed, then for Dubos the hand seeking to close it would forever have been teeming with pathogenic life. This was why his initial eulogy to the doctrine of specific aetiology was merely the prelude to a scathing attack. The doctrine, he suggested, had become more of a hindrance than a help in the quest to understand infectious diseases. “Few are the cases in which it has provided a complete account of the causation of disease”. “Despite frantic efforts” he pointed out, “the causes of many diseases remain undiscovered”. And whilst “it is generally assumed that these failures are due to technical difficulties”, in reality, “the search for the cause may be a hopeless pursuit because most disease states *are the indirect outcome of a constellation of circumstances rather than the direct result of a single determinant factor*”.¹¹ As he went on to note during a later work, *Man, Medicine and Environment*, these problems stemmed from the doctrine’s “artificiality”: “specificity” was “much less readily demonstrated in natural clinical situations than in experimental laboratory models”.¹² To capture *natural* aetiology “a new formulation of aetiological theory” was needed.¹³ And for him, only a multifactorial understanding of causation would be able to “bring scientific understanding a little nearer to the complexities of the real world”. “Multifactorial aetiology”, he suggested, was “the rule rather than the exception”.¹⁴

Dubos’ work on and around the issue of disease causation in humans serves to foreground an interesting, yet very rarely commented upon tension within the discipline of medical microbiology. It is generally assumed that the doctrine of specific aetiology – otherwise known as the “germ theory of disease” – holds all

medical microbiologists in its sway, as something akin to “the cornerstone of contemporary biomedicine”.¹⁵ Indeed, it is perhaps indicative of just how pervasive this assumption has become that Dubos’ original term “the doctrine of specific aetiology” has, over the years, been emptied of its critical and multifactorial intent to the extent that it now functions as a merely descriptive label in most contemporary textbooks.¹⁶ But as Dubos’ work seems to suggest, this is a doctrine that has never quite been able to eliminate all microbiological belief in the possibility that infectious diseases are caused by complex, processual interactions between various pathogens. Certainly it is true that some contemporary microbiologists tend to dismiss the possibility of a multifactorial aetiology as symptomatic of a lack of knowledge; of a failure to narrow things down properly and to get at which of the pathogens in question during a particular laboratory investigation is aetiologically culpable. As Lewis Kuller has noted, for example, “the concept of multifactorial aetiology of many diseases may be a measure of our ignorance of causality rather than a biological principle”.¹⁷ But, nevertheless, Dubos was not, and indeed is not, alone in believing in the possibility of multifactoriality. Ever since the birth of the doctrine of specific aetiology and the concomitant birth of the singular aetiological object, the multifactorial object has always been present as a possibility within the discipline of medical microbiology. Although any number of articles, commentaries, reviews or conference papers could be called upon to reinforce this point, it is perhaps instructive to focus on just two representative examples.¹⁸ Separated by over 60 years of disciplinary progress and development, they serve to emphasise the sheer persistence of the theory of multifactoriality. The first appears in the pioneering American virologist Thomas Rivers’ 1937 paper, “Viruses and Koch’s Postulates”.¹⁹ Writing of the emerging field of virology, he notes that, “for the progress of knowledge of infectious diseases . . . blind adherence to Koch’s postulates may act as a hindrance instead of an aid. For instance, the idea that an infectious malady can be caused only by the action of a single agent is incorrect, and, if [Frederick] Shope had adhered to old ideas, he would never have discovered that swine influenza as it occurs in nature is caused by the combined or synergistic action of two agents”.²⁰ The second example is taken from a chapter entitled “Diseases of unknown aetiology: the role of infectious agents” and published in the 2004 edition of the textbook *Infectious Diseases*.²¹ Therein, under the sub-heading “elusive associations and hidden pathogens”, its author, David Fredricks, probes away at the limits of the doctrine of specific aetiology, noting that:

Diseases may result from pathogenic microbial communities. Failure to identify all co-pathogens in the community will lead to spurious conclusions about disease causation. We are familiar with the paradigm in which each disease is caused by a single microbe. What if disease required the interaction of several microbes? In this setting, identification of a single pathogen may not reliably predict disease.²²

So, two possible theories of disease causation. And two possible aetiological objects. Both are plausible, both are possible, and both have their medical microbiological advocates. And yet, despite all of this, ours is a world defined almost entirely by the doctrine of specific aetiology. In order to start thinking about how this “resolution-into-singularity” is achieved as an empirical phenomenon, the next section presents the details of a moment during the 2003 SARS outbreak at which the possibility of a multifactorial disease started to emerge precisely as a possibility.

SARS: A “Normal” Disease?

In a “global alert” issued by the World Health Organisation (WHO) on 15 March, 2003, a new and emerging infectious disease was born. Whilst describing “a series of outbreaks of pneumonia in Viet Nam, Hong Kong Special Administrative Region, and China”, the phrase “severe acute respiratory syndrome” was used for the first time.²³ From a biomedical standpoint, however, the most striking thing about the alert is not so much its performative work, but the fact that references to aetiology, and the need to provide this new entity with an aetiological agent, abound. As the coordinator of the WHO’s outbreak response team, Dr. Klaus Stöhr, was to note some weeks later, the WHO’s initial response to SARS was built around the principle that “the unidentified causal agent could lead to an exceptionally dangerous outbreak”. In the view of “WHO epidemiologists and virologists, as long as the causal agent remained unknown, and no specific interventions against the agent were available,” the chances of SARS “establish[ing] endemicity” would increase exponentially. That was why, as Stöhr continued, the “identification of the causal agent” had been given “paramount importance in the overall containment strategy”. Indeed, just two days after the initial SARS alert, the WHO “set up a network of scientists from 11 leading laboratories around the world to expedite identification of the causative agent of SARS”.²⁴ Data soon began to accumulate. During a WHO organised press conference on 25 March, for example, Stöhr was able to report on how “these 11 laboratories in these nine countries have found already two very strong contenders, two viruses which are consistently isolated from many patients from very many different countries”.²⁵ The two viruses to which he referred were, respectively, a human

metapneumovirus from the family Paramyxovirus and the order Nidovirales, and a coronavirus of the family Coronaviridae and the order Mononegavirales. But for Stöhr, and indeed for the members of the network whom he sought to represent during that press conference, these were not aetiologically significant findings. The fact that more than one virus had been identified was not, in their opinion, evidence that a complex, multifactorial disease outbreak was in the process of developing. Already, Stöhr's metaphoric reference to "two very strong contenders" seems to be hinting at a belief in some kind of singularity to come. But there is no need for any deep rhetorical analysis here. For as he went on to confess, "we are all a bit puzzled by these results". And the "puzzlement" of Stöhr's collective "we" stemmed from the fact that "it is not normal that one disease is caused by two viruses". As a result, "research was ongoing" and "laboratories would have to strengthen their research activities".²⁶ The first indications that SARS was a "normal" rather than an "abnormal" disease were not long in coming. On 10 April, a WHO laboratory network team led by Thomas Ksiazek at the Centres for Disease Control and Prevention, Atlanta, USA, published the results of their aetiological studies in the *New England Journal of Medicine*. "A novel coronavirus associated with SARS" was one of the first papers to single out the coronavirus, and the coronavirus alone, as the aetiologically significant pathogen.²⁷

"It is not normal that one disease should have two causes . . ." What to make of such a statement? Certainly what I want to suggest we see here in Stöhr's normality is the silent, structuring influence of the germ theory of disease. And to judge from Stöhr's words, in the century that has elapsed since, as Dubos puts it, Robert Koch and his followers showed "by laboratory experiments that disease could be produced at will by the mere artifice of introducing a single specific factor – a virulent microorganism – into a healthy animal",²⁸ the theory has become so well established, so medically constructive, that it has also become, literally, unremarkable. That one disease had one pathogenic cause was simply a matter of biomedical fact for Stöhr. But then, if this is so, there might seem to be little to dispute about such a "normality". As the sociologist Bruno Latour has counselled, for instance, when talking about a cold, hard part of medical science, "we should shift our method like the scientists themselves who, from hardcore relativists have turned into dyed-in-the-wool realists. Nature is now taken as the cause of accurate descriptions of herself. We cannot be more relativist than scientists . . . Why? Because the cost of dispute is too high for an average citizen . . . Nature talks straight, facts are facts. Full stop".²⁹ Yet at this juncture it is worth reminding

ourselves that in this particular instance we are not at all “average citizens”, bereft of any medical microbiological allies. Standing alongside figures such as René Dubos and Thomas Rivers, Latour’s counsel can safely be ignored and Stöhr’s formulation explored in a little more detail. Indeed, as the next section of this paper seeks to demonstrate, the “abnormality” Stöhr so casually sought to dismiss – the idea that one disease might actually have more than one cause – is in fact nothing less than a “normality” when considered from the kind of aetiological perspective advocated by microbiologists such as Dubos and Rivers.

Koch and Winogradsky: the Singular and the Multifactorial

To develop this point about the indexical nature of the “normal” it is necessary to return to the founding moments of the primal aetiological controversy that flared during the late 19th century between Robert Koch, one of the founders of the germ theory of disease, and Sergei Winogradsky, one of the first microbiologists to develop a multifactorial way of thinking about the microbial world.³⁰ The aim in doing so will be to pave the way for a genealogical reading of the techniques and the practices that did, and, crucially, did *not* come to play a part in the laboratory work performed by Ksiazek and his colleagues during the 2003 SARS outbreak.

Firstly, then, consider Penn and Dworkin’s article “Robert Koch and two visions of microbiology”.³¹ Therein, they suggest that “emerging alongside the Kochian tradition in 19th century microbiology, was another competing, distinctive, and less conspicuous tradition associated with the name of Sergei Winogradsky”.³² What Penn and Dworkin suggest we see here in these “competing traditions” is “the rise of two distinctive modes of microbiological thought”: on the one hand, a Kochian tradition which they refer to as the “essentialist mode” – and, on the other hand, a Winogradskian tradition – which they refer to as the “processual mode”.³³ By essentialist “we mean, roughly, the view that conceived of microbial cells as *independent* entities possessing an *intrinsic anatomic and physiological scenario*, knowledge of which would be adequate for an understanding of their behaviour”.³⁴ Robert Koch and the essentialist medical microbiological school that he founded “advanced two separate but related criteria” in order to reach their singular understanding of aetiology. The first of those criteria was the existence of “fixed and immutable bacterial species”.³⁵ Microbes were, in other words, to be understood as basic, indivisible units of life. But in addition to the notion of morphological identity came the suggestion that “a causal bond held between differentiable pathogens

and specific diseases".³⁶ Coupled together in this way, they were criteria that enabled Koch to envisage medical microbiology as a discipline of *singularity*; a discipline that would seek to isolate distinct species of bacteria, and thus, in doing so, isolate distinct, and very singular, aetiological objects. For the "essentialist", then, aetiological culpability was to be established via the isolation of a highly specific clonal grouping of microbes.³⁷

The "processual" view, in contrast "emphasised process and sequential interaction as a persistent feature of microbial phenomena. In this view, furthermore, single cells are always located in cell populations, and their physical and chemical properties derive, accordingly, from various *interactive processes* within the population".³⁸ Whereas Koch based his studies upon the morphological form of individually existing microbes, Winogradsky based his upon the notion of interaction between various different types of pathogen. It is true, of course, that like Koch, Winogradsky believed that the orderly investigation of bacteria required the idea of "fixed and immutable bacterial species".³⁹ But whereas from Koch's standpoint individual microbial "form" amounted to "a generalised description of specific and invariant varieties of microbes", it was, for Winogradsky, a convenient designation for "intricately different constellations of microbes competitively adapting to varying environmental conditions".⁴⁰ Indeed, these deep philosophical differences led to two very different theoretical conceptualisations of form: the Kochian "grouping" and the Winogradskian "biotype". Writing of his identification of "distinct bacteric forms" during a study of various traumatic infective diseases, for instance, Koch could note that whilst "observ[ing] their situations and grouping":

I study not only the individual alone, but the whole group of bacteria, and would, for example, consider a micrococcus which in one species of animal occurred only in masses (i.e., in a zooglea form), as different from another which in the same variety of animal, under the same conditions of life, was only met with as isolated individuals.⁴¹

As this extract unfolds, it becomes clear that Koch's conception of a "grouping" of bacteria was precisely that of his isolated, individual microbes clustered together with others of the same species. A *clonal* grouping. For him, difference was a problem, not an analytic insight. In Winogradsky's work, however, a "biotype" appears as something akin to a Latourian hybrid.⁴² Nature, for Winogradsky, was not made up of singular, monadic entities. On the contrary, under natural conditions, *in vivo* as it were, microorganisms lived as elements within a greater biotype: nomadic communities in which cooperation and competition were characteristic and interactions between pathogenic organisms were extremely complex.

Indeed, competition was the key natural phenomenon for Winogradsky. The chemical activities of a microbial organism depended upon its complex and varied relationships with other organisms. Within a biotype, process and sequential change were persistent features of microbial phenomena. As he noted in one of his major philosophical expositions, because “the great majority of microbes are found in nature and carry out their normal activities . . . in mixed populations”, microbiologists seeking an understanding of microbial life in “nature” would need “to see the microbe in question, *engaged in the life contest with other microbes*”.⁴³

For Koch, the differentiating characteristics of solitary organisms and the physically and physiologically independent pathogen, whereas for Winogradsky the associative dependencies of a mixed population and their communal interrelations.⁴⁴ The differences between these two “visions” of microbiology were profound. Under the essentialist assumptions of Koch, microbes were to be envisaged as singular, pure and distinct entities, whilst under the processual assumptions of Winogradsky, they were to appear as multiple, impure and interactive.⁴⁵ On the one hand, singular aetiology as “normality”, and on the other hand, multifactorial aetiology as “normality”. But if this dispute initially stemmed from crucial and wide ranging philosophical differences, it ultimately came to affect the ways in which both microbiologists intervened within, and upon, the microbial world. For an essential symptom of those differences was the technical issue of how to try and recreate the *in vivo*, the living microbial world, within the *in vitro*, those various artificial systems housed within research laboratories. Both practitioners agreed that the technique of the culture was best suited to playing the role of “a body outside of the body” – once extracted from their hiding places within diseased human bodies and forced to grow upon the nutrient rich surface of a culture, microbes could be exposed, very directly, to the microbiological eye.⁴⁶ Where Koch and Winogradsky differed, however, was over the issue of how to extract samples from diseased bodies prior to their inoculation into a culture medium.

It was in a paper entitled “Methods for the study of pathogenic organisms”⁴⁷ that Koch was to stake out his own method of isolating pathogens *in vitro*. And, therein, one can begin to understand the technical, material issues separating Koch’s inoculum from Winogradsky’s. Koch, thinking solely in terms of singular aetiology and the isolated pathogen, developed a technique that was driven by the need, as he put it, “to rid oneself of the uninvited guest”.⁴⁸ Without such an act of expulsion, samples “would reveal under the microscope from the beginning, a tangled mixture of different shapes and sizes”.⁴⁹ And that was why his method for the prepa-

ration of an “untangled” sample, proceeded as follows: “the organism to be cultured is seeded by taking a flamed needle or platinum wire, picking up a very small quantity of the liquid or substance containing the organisms, and streaking this in three to six cross lines on the gelatine surface . . . the expression ‘inoculation’ for this operation seems appropriate”.⁵⁰ “Streaking”: a form of separation; of sorting aetiologically significant from aetiologically insignificant pathogens (see Figure 1, below). In short, a way of showing the “uninvited guest” the door.

But what if, during that streaking process, “contaminating colonies” started to appear, with the singular pathogen becoming entangled with others?⁵² For Koch this was not a problem. A new “seed” stock of one “pure” colony could be taken and inoculated onto a new culture. And, during their transfer to a new culture, any “contaminating colonies could be easily removed”,⁵³ as “within a few days the pure cultures have developed to their maximum extent and can be inoculated further”.⁵⁴ If the taking of a “seed” did not allow for separation, then:

It is only necessary to take a flamed needle and remove some blood from the opened heart or a convenient blood vessel and streak it a few times on the nutrient gelatine. There will occur growth in colonies of several types of microorganisms, among which will be a greater or lesser number of pure, characteristically matlike and granular colonies which can be characterised under the microscope . . . It will be quite easy to culture these further in pure culture. In this case the number of foreign organisms is at a minimum, so that it is quite easy to isolate the pure colonies of the appropriate organism.⁵⁵

However, as Koch continued:

Even if this situation were reversed and the sought-for organisms were in the minority, it would still be possible to have success. Although here it would not be as

Fig. 7.2 The commonly adopted pattern of plating-out on solid medium. The area A is the well, and successive series of strokes B, C, D and E are made with the loop sterilized between each sequence.

Figure 1: The streak-plate method.⁵¹

easy, it would be just as certain. It is only necessary to dilute the bacterial mixture considerably and then make a large number of streaks. In such circumstances it is advantageous to inoculate into the still liquid gelatine, in order to spread the various germs over a wide area, and then pour it on the slides and locate the colonies which develop under the microscope.⁵⁶

Unsurprisingly, Winogradsky's approach to the development of samples for inoculation was markedly different. Starting from the premise that interactions between microbes were complex, processual and dynamic, Winogradsky "never ceased to emphasise the limitations of the pure culture [i.e. Koch's] method".⁵⁷ For him, the problem with Koch's strategy of removing the "uninvited guest" was that it "eliminated the most essential ecological factor, I mean competition, since it is precisely this factor that determines the distribution of the processes implemented by microbes in nature, and automatically directs the succession of these processes".⁵⁸ It was again with the Kochian school of bacteriology in mind that he was to note how "some bacteriologists" (i.e. those who persisted in using pure inoculums to study microbial life) "deal with hothouse varieties of bacteria, far removed from their naturally occurring progenitors, and would hardly recognise them when found in their natural milieu".⁵⁹ For Koch, the *in vivo* could be considered to be as pure and orderly as the *in vitro* environment of the culture. But for Winogradsky the challenge was to develop a method that could recreate the unruliness, the mess, of the *in vivo* as closely as possible in the *in vitro* environment: "the method for investigation of actual processes mediated by microbes in nature should be based on the study of microbial communities as a whole, in nature, rather than on the study of species isolated from nature".⁶⁰ The method of inoculation he built around those principles was the "elective", or "mixed", method, in which microbial communities were allowed to develop together. Introduced during his studies of nitrifiers in the late 19th century, and described in an 1895 paper devoted to the discovery of free living nitrogen fixing bacteria, it was intended as "a model of natural processes".⁶¹ Prior to the cultivation of microbes, the microbiologist's task was to take the culture in question "directly from its natural habitat" and "to avoid exposing the subsequent inoculum to strong stresses during isolation, including isolation on media to which it was not adapted".⁶² These are precisely the kind of suggestions that would have horrified a Kochian during the 1890s. Nowhere here is there to be found any talk of purity, or of the need to remove "the uninvited guest". "The culture will be elective", stated Winogradsky, "if it is favourable for the detection of the sole function . . . by supporting the microbe in question, engaged in the life contest with other microbes".⁶³

Whereas Koch's inoculation technique assumed purity – the indivisible microbe existing alone or within clonal populations – Winogradsky's technique stressed impurity and disorder – the gregarious, perhaps even competitive microbe, existing within a nomadic community of other, disparate microbes. For Koch, an inoculum freed from all “contamination”, a white spot of propriety constituted through an expulsion of the “uninvited guest”, but for Winogradsky, the inoculum as a disorderly fluid, a space of difference and multiplicity.

SARS and the “Isolation” of the SARS Coronavirus

In this section, the task will be to make clear how the previous discussion of Robert Koch and Sergei Winogradsky relates to the isolation, by Thomas Ksiazek and his colleagues, of a coronavirus during the 2003 SARS outbreak. My approach will be to develop a reading of Ksiazek et al.'s article, “A novel coronavirus associated with SARS” (henceforth NCA) that can tease out the genealogical connections between the 21st century cell-culture work reported therein, and the original methodological presuppositions of the culturing technologies developed during that founding, 19th century controversy.

In NCA's abstract, it is noted how “a novel coronavirus was isolated from patients . . . and the evidence indicates that this virus has an etiologic role in SARS”.⁶⁴ Clearly, then, “isolation” marked a crucial moment in the research process. But what kind, or kinds, of laboratory diagnostic technology performed this crucial work of “isolation”? Despite the paper's references to various diagnostic techniques – cell-cultures, electron microscopes, enzyme linked immunosorbent assays, reverse transcriptase polymerase chain reaction systems, and so on – one passage in particular makes clear that it was the cell-culture technique alone that was crucial for those initial “isolation” attempts: “the identification of this novel coronavirus relied on classic tissue-culture isolation to amplify the pathogen and then on electron-microscopical studies to identify the type of virus”.⁶⁵ “Classic tissue culture”. As if the time of medical microbiology were “crumpled” and “folded”, it is perhaps possible at this juncture to see how the technique of culturing brings Ksiazek and his 21st century colleagues into close proximity with the late 19th century methodological work of Koch and Winogradsky.⁶⁶ But how close? And to which one of these two historical figures?

Consider, firstly, the following extract, taken from the “methods” section of NCA:

To identify viruses associated with SARS, we inoculated a variety of clinical specimens (blood, serum, material from oropharyngeal swabs or washings, material from

nasopharyngeal swabs, and tissues of major organs collected at autopsy) onto a number of continuous cell lines, including Vero E6, NCI-H292, MDCK, LLC-MK2, and B95-8 cells. All cultures were observed daily for cytopathic effect. Maintenance medium was replenished at day 7, and cultures were terminated 14 days after inoculation.⁶⁷

Over their many years of use within the microbiological sciences, cell-culture methods have become *entrenched* methods. That is why Ksiazek's research team did not feel the need to detail their methodology at any great length: a few basic references are given, but that is all. Perhaps the only glimpse of human hands and human ingenuity comes with the use of the transitive verb "to inoculate". And yet, even there, nothing is written about the specificities of the process. An entire context of discovery slips away into the shadows created by this verb. So in order to "get at" the ways in which this diagnostic activity effected the visualisation of a singular coronavirus, one has to take a step backwards, to a position upstream in the scientific knowledge production process prior to NCA's publication. And as good an upstream starting point as any here is the laboratory manual *Jawetz, Melnick & Adelberg's Medical Microbiology*.⁶⁸ In a section therein, entitled "Purification and Identification of Viruses",⁶⁹ it is noted that the "starting material" for studies of viruses "is usually large volumes of tissue culture medium, body fluids, or infected cells". But as the section goes on to make clear, those starting materials have to go through a process of "purification" prior to their actual inoculation onto a cell-culture:⁷⁰ "pure virus *must* be available in order for meaningful studies on the properties and molecular biology of the agent to be carried out".⁷¹ The question of why purity is deemed such an imperative can, for the moment, be left to one side. Here it is enough to relate this procedural information back to the isolation work reported in NCA. For what Ksiazek and his research team make clear is that they "received clinical specimens from [SARS] patients in several countries" before then testing them in the hope of "identify[ing] a range of potential pathogens" and, perhaps even "the etiologic agent of the outbreak".⁷² Given this information, it can safely be assumed that one of their first research tasks would have involved some kind of "purification" of those "received clinical samples".

So what might that purification have entailed? Consider the most recent edition of the "virologist's bible", *Fields Virology*.⁷³ Included within chapter 17, "Diagnostic Virology",⁷⁴ is a small subsection entitled "specimens for viral diagnosis".⁷⁵ Therein, it is noted that "the likelihood of making a specific viral diagnosis depends largely on the quality of the specimen that is received in the laboratory". Important variables are listed as "the type of specimen, the quality and amount of specimen material obtained, and the time and

conditions of transport to the laboratory".⁷⁶ NCA itself does in fact provide a little information on the *first* variable, the type of specimens received by Ksiazek's research team, noting that they were "nasopharyngeal swabs and tissues of major organs".⁷⁷ And, despite the fact that the text omits any reference to the quality of the specimens (variable 2), or the ways in which they were prepared for transport to, and inoculation within, the laboratory (variable 3), such information is not hard to come by. For as has already been mentioned, Ksiazek's research team were working as part of the WHO led laboratory network. As a result, they were using samples prepared and transported along lines set out in the WHO's own SARS laboratory recommendations. Table 1 (below), for instance, is taken from those recommendations.⁷⁸

Given that NCA refers to its use of "nasopharyngeal specimens", and given too that the WHO recommendations suggest such specimens as "the specimens of choice for the detection of respiratory viruses",⁸⁰ I want to devote some attention to their collection methods:

Have the patient sit with head tilted slightly backward. Instill 1 – 1.5 ml of *non-bacteriostatic saline* into one nostril. Flush a plastic catheter or tubing with 2–3 ml of *saline*. Insert the tubing into the nostril parallel to the palate. Aspirate nasopharyngeal secretions. Repeat this procedure for the other nostril.⁸¹

Already, at the very first stage of specimen collection, a process of "purification" has begun. "Nonbacteriostatic saline", "saline" – agents that cause death and lysis in bacterial, *but not viral life forms*. Indeed, as one laboratory manual concludes "a preliminary purification [at the level of the clinic] will remove most non-viral matter".⁸² Destruction of unwanted bacteria, the "normal" bacterial flora that inhabit the nasopharynx, is deemed to be of paramount importance here. As aetiologically insignificant microbes, they are

Table 1: WHO Sampling strategies⁷⁹

Type of specimen	Method	Medium/container/shipment
Nasopharyngeal or oropharyngeal	Swab: use only sterile Dacron or rayon swab with plastic shaft	Sterile vials with viral transport media Ship on ice (+4°C)
Tissue (biopsy, autopsy)	Lung, upper airway	Sterile container with viral transport medium or saline. Fresh frozen: -70°C

to be treated as nothing more than potential “contaminants”.⁸³ Already, then, there would seem to be hints of the germ theory of disease marking this process – for what are “contaminants” if not “uninvited guests” by another name; the interactive, multifactorial partners that might interfere with a search for the purity of the singular virus?

But what now of variable 3, preparation of those samples for transport? The medium for storage advocated by the WHO was “sterile vials with viral transport media [henceforth VTM]”.⁸⁴ Why? Because as one review article puts it, clinical samples collected from the nose can potentially still be “contaminated with microbial flora”.⁸⁵ If this metaphor of contamination is suggestive of what *might* have to happen to the flora, then another laboratory manual makes its fate even clearer: “normal endogenous flora *must* be suppressed . . . contaminating organisms must be removed during sampling”.⁸⁶ This extract also explains why the WHO recommended that such samples be placed in a sterile vial with a VTM: VTMs “contain antibiotics” along with “a buffered salt solution, and a proteinaceous substance (such as albumin, gelatin, or serum), and a pH indicator”.⁸⁷ These antibiotics and “nonbacteriostatic saline” solutions, then, marked the start of a decontamination, or purification, process that would have continued when the specimens arrived at Ksiazek’s laboratory. But even at this stage, there is only one passage from NCA in which any hint is given as to what the laboratory processes of purification might have entailed: “given the serious nature of SARS and the suggestion of person-to-person transmission, it was decided to handle all clinical specimens in a biosafety level 3 environment. All division into aliquots, pipetting, and culture attempts were performed in laminar-flow safety cabinets in a biosafety level 3 laboratory”.⁸⁸ It seems to have been deemed more important to alert readers as to *where* “handling” and “culture attempts” had taken place, rather than *how* they had taken place. And so, once again, it is necessary to step outside NCA in order to understand the practices detailed (however briefly) therein.

Turning to the laboratory manual *Jawetz*,⁸⁹ the following information is given under the heading “Virus culture: preparation of inocula”: “bacteria-free fluid materials such as cerebrospinal fluid, whole blood, plasma, or white blood cell buffy coat layer may be inoculated into cell-cultures directly or after dilution with buffered phosphate solution (pH 7.6)”.⁹⁰ However, it is also noted that materials containing “bacteria (throat washings, stools, urine, infected tissue, or insects) must be *inactivated or removed* before inoculation”.⁹¹ The nasopharyngeal swabs received by Ksiazek’s research team were obviously materials of this latter type. They might *still*

have been “contaminated”. Processes of “inactivation” or “removal” thus had to be completed in the laboratory rather than the clinic. But how would this have been achieved? Although “specimen processing guidelines differ from laboratory to laboratory” it is nevertheless true that “most laboratories clarify certain sample types (e.g., respiratory samples) as follows prior to inoculation into cell-cultures”:⁹² “the transport medium tube is vortexed, the swab is discarded, the liquid medium is centrifuged . . . material may [then] be liquefied in antibiotic containing medium and filtered through a 0.45- μ m filter. The end product is a supernatant fluid that can be used to inoculate cell-cultures”.⁹³ Both the nonbacteriostatic saline and the VTM, it would seem, were merely holding operations. For it is here, with these practices, that the most explicit form of purification unfolds. In virological terms, “to vortex” something is to release the contents of the swab into a fluid solution. But it is the use of a *differential centrifuge* that is perhaps of most interest here. In a differential centrifuge:

A suspension is centrifuged at low speed (not >2,000 rpm) for 10 minutes to sediment insoluble cellular debris . . . It is a convenient method for removing many bacteria from heavily contaminated preparations of small viruses. Bacteria are sedimented at low speeds that do not sediment the virus, and high-speed centrifugation (<2,000 rpm) then sediments the virus. The virus-containing sediment is then re-suspended in a small volume.⁹⁴

In this way not only *bacteria*, but also *fungi*, *cells*, *blood mucus*, *fibres*, *etc.*, are pelleted into the bottom of the spun tube, while the viruses in the “suspension”, which will not be spun down by the g-force generated by most general laboratory centrifuges, can be collected. A fascinating form of distribution. Much effort in constructionist science studies over the years has been devoted to grappling with the question of how controversies close.⁹⁵ The end result has usually been a suggestion that things *could have been* otherwise; that alternative constructions of reality *might* have been possible in the past, but that they vanished before they ever could fully blossom. In the case of this differential centrifuge, however, it is possible to suggest that there is actually a *co-existence* of two different aetiological realities – the singular pathogen and the interactive, multifactorial pathogen. The only caveat that has to be added here (and it is an important caveat) is that the technology itself manages to distribute the two realities into different, but co-present “sites”. At this stage, it seems as if two different yet equally possible aetiological realities could have been separated by less than a few millimetres of murky liquid.⁹⁶

This tension between distance and proximity can be seen elsewhere too. The “liquid medium” referred to above would have been

treated with “bactericidal agents”, either *antibiotics* or even *ether* if the latter had been considered non harmful to the virus in question.⁹⁷ These agents would have been added to the supernatant in concentrations of 10–15%. In addition, it is possible that “extensively contaminated material” from the nasopharyngeal aspirates would have been “liquefied in antibiotic-containing medium and passed through a *filter*”.⁹⁸ The extract presented above suggests the use of a 0.45- μm (micro-metre) size filter, but in fact the size of the filter would have been up to Ksiazek and his colleagues (the standard sizes are 0.45- μm 0.65- μm and 0.90- μm). Irrespective of the final choice, however, the function of the filter is clear: to separate smaller viral particles from the larger bacterial “*debris*”:⁹⁹ bacterial life forms, measuring between 1 and 5 micrometres in diameter, would not have found their way through the filter. Again, a form of distribution in which the difference between the singular and the interactive, multifactorial pathogen might, ultimately, have been determined by a pore less than a micrometre in diameter.

Before moving on, however, it is important to make clear that I have not based the analysis around nasopharyngeal sampling procedures because they are uniquely touched by this purification process. If we look briefly at the recommended methods for preparing “tissue samples” (see Table 1, above) similar practices are advocated. The method of collection suggested by the WHO was simply “lung/upper airway”, meaning, in effect, that physicians could use their own individualised collection protocols. Once collected, the samples were to be transported to Ksiazek’s laboratory in a VTM. Upon arrival, the tissue samples would have been “washed in media or sterile water, minced into small pieces with scissors, and ground to make a homogeneous paste”.¹⁰⁰ That step would then have been followed by “the concentration of the virus particles by precipitation with ammonium sulphate, ethanol or polyethylene glycol or by ultra filtration”.¹⁰¹ And finally, the resulting suspension would either have been passed through a “millipore type membrane filter of cellulose acetate or similar inert material to separate smaller viral particles from the larger *debris*”, or, alternatively, “centrifuged at low speed (not >2,000 rpm) for 10 minutes”.¹⁰² These, then, were some of the “purification” practices that had to be performed before Ksiazek and his research team could isolate and photograph a singular coronavirus, isolated from anything but itself and its culture system (see Figure 2, below).

Purification and the (Lost) Possibility of Multifactoriality

But what to make of this purification process from a multifactorial perspective? If the process through which samples had passed had

Figure 2: The cell-cultured SARS coronavirus.¹⁰³

been designed to purify samples of all *laboratory* contaminants; that is, entities that had contaminated samples *after* their collection from the body, then there would be little for a multifactorialist to find troubling about it. But laboratory contaminants were not the only contaminants being purified. Bacterial entities from the same bodies, and the same sites within those bodies as any potentially viral entities, were also being treated as “contaminants” and “impurities”. And, as a result, it is difficult to see how *any* but viral particles could have survived in the clinical samples received by Ksiazek’s laboratory. Of course, from Dr. Stöhr’s perspective, it is easy to see why bacterial contaminants were treated precisely as “contaminants” – if one disease *normally* has one cause, then inevitably, with a disease like SARS, in which none of the patients were responding to antibiotic treatment, only singular viral particles were likely to be of interest. But, nevertheless, from a multifactorial perspective this starts to seem very much like a self vindicating style of practice.

To explain why, it is useful to recall Sergei Winogradsky’s suggestion that “the great majority of microbes are found in nature and carry out their normal activities not in pure cultures, but in mixed populations”.¹⁰⁴ For him, the “most essential ecological factor [was] competition, since it is precisely this factor that determines the distribution of the processes implemented by microbes in nature, and automatically directs the succession of these processes”.¹⁰⁵ As a consequence, and as René Dubos might have noted, “the complexity of most ecological systems render it difficult to single out any one particular component of the system as playing a role of unique importance in the causation of disease”.¹⁰⁶ Indeed, perhaps the very

possibility of multifactorial aetiology is reflected in the amount of rhetorical work that laboratory manuals have to perform in order to draw some kind of dividing line between “purity” and “impurity”:

Specimen from sites with a *normal flora* (e.g. upper respiratory tract, faeces, genital specimens) – are cultured on selective media *designed to suppress normal endogenous flora but allow likely pathogens to grow* . . . Sputum and urine specimens are sometimes described as ‘*clean contaminated*’, because normally both should be sterile, *although they may become contaminated during sampling*; sputum by upper respiratory tract flora or urine by perineal flora. Some ‘*contaminating organisms*’ may also cause contamination (e.g. pneumococci from the pharynx may contaminate sputum). Quantitative culture is performed to help distinguish *contamination* (low numbers of bacteria/several different bacterial species) from *infection* (high numbers of single bacterial species).¹⁰⁷

“Normal flora”, “clean contaminated”, “contamination versus infection”: from a Winogradskian perspective these distinctions make no sense. And yet what they, and the practices they describe, serve to achieve in the case of a disease like SARS is the removal of all that might have been of interest from a multifactorial perspective: the bacterial life forms that coexisted with, and perhaps even interacted with, viral life forms. Even the slightest possibility that the samples in question might have been taken from patients infected with an interactive assemblage of pathogens was suppressed. Might those “contaminants” and “impurities” have played their parts in the aetiology of SARS? I cannot answer this question. But rather more importantly, neither can Ksiazek or his research team.

These practices of *bacterial* purification are explicit and obvious. But there might also have been implicit processes of purification at work here on any *viral* matter included within the samples. Consider the information provided in Table 1 regarding the “method” for obtaining samples. There, reference is made to the need to keep samples cool until a time when cell-culture inoculation can begin. Such attention to temperature is required because “in contrast to molecular or serologic detection techniques, which can often identify virus in the absence of intact virus . . . viral isolation techniques require intact, infectious virus”.¹⁰⁸ And to preserve the viral titer and viral infectivity of culture specimens:

The specimen should be transported to the laboratory as quickly as possible after specimen collection to ensure its integrity. When immediate transport is not possible, the specimen should be kept refrigerated or on wet ice. In general, it is never a good idea to hold specimens at room temperature, and if a delay or more than 24 h in transport of specimens is anticipated, specimens should be rapidly frozen to –70C or lower and transported to the laboratory on dry ice.¹⁰⁹

This represents a generally accepted method for preserving the viral titer and viral infectivity of clinical samples during storage.¹¹⁰ But it

is not difficult to start picking some holes in it. Elsewhere in the microbiological literature, for instance, it is readily admitted that “a number of clinically important viruses are labile and will not survive prolonged transport”.¹¹¹ Their instability has to do primarily with the issue of temperature. Whilst some may be preserved through freezing or cooling, as a whole host of laboratory manuals seek to point out, others may not:

Some viruses can be completely destroyed by freezing.¹¹²

The recovery of some viruses may be greatly affected by freezing (e.g., cytomegalovirus, varicella-zoster virus, and respiratory syncytial virus).¹¹³

The recovery of some viruses is seriously compromised by any freezing . . . recovery of cytomegalovirus by culture is very unlikely if the time of transport is 24 hours or greater, regardless of whether the sample is at room temperature or 4C.¹¹⁴

This issue is of direct relevance to the case at hand. Given that Thomas Ksiazek’s laboratory in Atlanta, USA received its “clinical samples” from “patients with SARS in Singapore, Bangkok, and Hong Kong”,¹¹⁵ those samples would have spent some time in storage, and thus at low temperatures. It is possible to get at what is at stake here by focusing on an example from one of the textbook accounts cited above: respiratory syncytial virus (RSV). Given that RSV is known to cause the kind of symptoms that the majority of SARS patients were presenting with, might it not have been there, within clinical samples, before being “purified” out during the storage and transportation of those samples?

This is entirely possible. But from a multifactorial perspective it is also possible to go a little further than this, bringing the textbook accounts back into contact with the kind of microbiological knowledge that they seem to accept, yet ignore. Note, for instance, how the accounts cited above focus entirely on *known* viruses. And yet, once one accepts, as these manuals and textbooks seem to have accepted, that viruses are unstable and unstable in a variety of different ways, then why draw the line at the known? For all that they are admitting is that known viruses are labile, and that, with some changes in temperature, known viruses can either be protected or, in some cases, destroyed. The possibility that hitherto *unknown* viruses, just like the SARS coronavirus, might also be labile, and labile in different ways to known viruses, is simply not considered (here, for example, the role of an agent such as “ether” during the inoculation process could be questioned – if it is known to be harmful to viruses such as enteroviruses and vaccinia, and is thus not used when such viruses are suspected, there is no reason to suppose that it might not be harmful to currently unknown viruses).¹¹⁶ Yet, nevertheless, it is a definite possibility. After all, the

SARS coronavirus was unknown prior to its isolation by Ksiazek and his colleagues. Indeed, since the 1980s at least ten new viruses have been discovered. So at the very least it seems plausible to speculate, just as many medical microbiologists do, that many viruses remain unknown precisely because of their instability. As one research article points out, for instance, “the aetiology of the majority of respiratory tract infections is thought to be viral, yet in only 40% of cases can a viral agent be identified . . . this suggests that previously unidentified viruses may be circulating”.¹¹⁷ And as the microbiologist David Fredricks has noted, “conventional microbial detection technologies may miss unconventional microbes”.¹¹⁸ Interestingly too, for Fredricks our current knowledge of viral life can best be understood through an agricultural metaphor: “the low-hanging fruit has been picked and the remaining fruit will require more work and some technical innovation to grasp a more elusive harvest”.¹¹⁹

Contemporary Medical Microbiology . . . and Competing Styles of Practice?

Microbes as “low-hanging fruit”? An interesting metaphor given that it has been used once before by a microbiologist attempting to describe a general logic of discovery within the medical microbiological sciences. Writing nearly a century before Fredricks, in 1909, Robert Koch was to note how:

New methods [of pure culturing] proved so helpful and useful in dealing with various problems that one could regard them as the keys for the further investigation of microorganisms, at least insofar as they relate to medicine . . . In a rapid sequence, my colleagues and I were successful in discovering the cause, and thereby the aetiology, of a number of infectious diseases. These included the wound infections, tuberculosis, cholera, typhoid, and diphtheria. Once the appropriate methods had been found, these discoveries fell into our laps like ripe fruit.¹²⁰

“The keys for the further investigation of microorganisms” that would allow discoveries to fall “like ripe fruit” into the laps of microbiologists. Is it not possible to see those same “keys” being turned in NCA? For Koch’s sterilisation procedures may we not read “the purification process”? And for the “streak plating” method, antibiotics, ether, the centrifuge and the microfilter? (see Figures 3 and 4, below).

If these links can be accepted; if the time of medical microbiology really is as “crumpled” and as “folded” as they seem to be indicating, then perhaps it is possible to suggest that modern 21st century medical microbiology has never quite managed to break free from late 19th century Europe. Via the medium of the cell-culture it is

possible, at the very least, to trace *a direct line of descent*, drawing these apparently distant periods into close proximity with one another.¹²³ And it is here, at this stage of the discussion, that talk of a distinctive Kochian “style” is apt. For in a sense, the performance of the aetiology of SARS as singular can be understood as the end result of a particular “style of practice”. This is a term I borrow from the work of the philosopher Ian Hacking.¹²⁴ There, it is used to put forward an “explanation” for the fact that “despite our recent enthusiasm for refutation and revolution”, an “extraordinary

Figure 3: Koch's photomicrographs of cultured bacteria (1886–1887).¹²¹

Figure 4: Ksiazek's electron-micrograph of cultured SARS coronavirus (2003).¹²²

amount of rather permanent knowledge” has accumulated within the laboratory sciences.¹²⁵ Hacking’s claim is that “as a laboratory science matures, it develops a body of types of theory and types of apparatus and types of analysis that are *mutually adjusted to each other*”.¹²⁶ Styles of practice, then, are self vindicating entities “in the sense that any test of theory is *against apparatus that has evolved in conjunction with it* – and in conjunction with modes of data analysis”.¹²⁷ As Hacking notes elsewhere, and in more detail:

Theories are not checked by comparison with a passive world with which we hope they correspond. We do not formulate conjectures and then just look to see if they are true. We invent devices that produce data and isolate or create phenomena, and a network of different levels of theory is true to these phenomena. Conversely, we may in the end count them as phenomena only when the data can be interpreted by theory. Thus there evolves a curious tailor-made fit between our ideas, our apparatus, and our observations.¹²⁸

For Hacking, then, such “styles of practice” allow for a degree of epistemic stability in the laboratory sciences. It seems to me that a similarly self vindicating style can be seen at work as we move from SARS patient sample to inoculum, and as we move, simultaneously, from the possibility of either a singular or a multifactorial aetiology to the certainty of singular aetiology, and a singular aetiology alone. In other words, the discovery of one single causal agent, a coronavirus, in a discipline where it was held as “abnormal” for one disease to be caused by more than one pathogen, was very far from being a serendipitous occurrence. On the contrary, there was only ever one possibility on offer here: Ksiazek’s cell-culture work enabled the simultaneous *production* of a singular, Kochian virus and the *suppression* of any and all possibility of a multifactorial, Winogradskian virus. Put simply, if the germ theory of disease has evolved into a style of practice in the medical microbiological sciences, entwining itself with the method of cell culturing, the theory of multifactoriality has remained just that: a theory bereft of methods.¹²⁹

And yet, consider for one final time, David Fredricks’ previous reference to microbes as “ripe-fruits”. Where once those ripe, singular fruits could be described by Koch as having *fallen* into the laps of microbiologists wielding the “appropriate methods”, for Fredricks, writing nearly a century later, things seem to have changed. For as the low hanging branches have been cleared, microbiologists have been left to gather their harvest from higher and higher branches. “Grasping this more elusive harvest”, as Fredricks suggests, “will require more work and some technical innovation”. Are Koch’s “appropriate methods” no longer so appropriate? Are “technical innovations” required because the fruits produced by those higher

branches no longer allow themselves to be moulded into the shape of a singular aetiology? For some practitioners, faced with a dwindling harvest, these questions now seem worth asking.¹³⁰ Indeed, in an attempt to explain why “microbe-disease associations may be missed”, Fredricks himself makes something of a “call to arms” to other microbiologists. “We are familiar”, he notes, “with the paradigm in which each disease is caused by a single microbe. What if disease required the interaction of several microbes? In this setting, identification of a single pathogen may not reliably predict disease”.¹³¹

The (In)stability of the Present?

Right now, it would seem, a singular style of practice defines the choices available to medical microbiologists, making it easier to ignore the possibility of the interactive, multifactorial pathogen than to pause and explore it. But what of the stability of that “right now”? Might the moments that have been recovered in this paper prefigure the kinds of moments that will, one day, have their significance discussed by medical microbiologists? These are some of the questions I want to touch upon in this, the final section of the paper. To do so I begin with a discussion of some recent modifications to the technique of cell-culturing in the medical microbiological sciences; modifications that have the potential to change what it means to identify, observe, diagnose and control an “infectious disease”.

In a recent microbiological textbook, reference is made to “the standard cell-culture”, but also to something called the “mixed cell-culture”.¹³² Under the latter heading we learn that “the most recent significant development in virus isolation methodology is the use of a mixture of cells in a shell vial format”.¹³³ “Up until recently”, the text continues, “the choice of cells has been focused on the ability to isolate and identify viruses that have a common pathological presentation, such as enteroviruses or respiratory viruses”.¹³⁴ One specific pathogen, one specific lesion. One disease, one cause. So far so singular. But the “distinctive thing”¹³⁵ about mixed cell-cultures is that “the cell mixture *allows for a broader range of viruses to be isolated in a single culture*”.¹³⁶ And, what is more, the inoculums used do not depend on the removal of Robert Koch’s “uninvited guest”. Interestingly, the trope of “the cocktail” – which would no doubt have horrified Robert Koch – has begun to appear within descriptions of this mixed culture technique:

Techniques involving combinations of different cell types grown together as a single monolayer in a vial . . . have been applied for the detection of several viruses in the same vial. Culturing for the *simultaneous detection* of adenovirus, CMV, and HSV in

the same shell vial has been approached using a mixture of . . . cells in the cell monolayer and staining with a *cocktail* of adenovirus, CMV, and HSV antibodies.¹³⁷

Is it possible to see the “keys” to the future development of a multifactorial style of practice here in this extract? The possibility of a interactive, multifactorial pathogen, co-existing with other pathogens, and falling into the laps of microbiologists? Certainly, for the Winogradskian instructions to “take a culture directly from its natural habitat” and “to avoid strong stresses during isolation” it might be possible to start reading of the “several viruses in the same vial”, “simultaneous detection” and the “cocktail of . . . antibodies”.

But one final question: the textbook extract cited above suggested that this had all begun to happen “recently”. So how recent is recently? The references included in that text, along with other references I have been able to find, are all to research articles that date from the early 2000s.¹³⁸ The irony, it seems, is that the 2003 SARS outbreak, which came to be enacted as an utterly singular disease, emerged at a moment in time when a slight move away from the use of a Kochian culture technique was taking place within the field of medical microbiology. But what should we *really* strive to see here? A “slight move away” from the past? Something of little importance? Perhaps. But what if we look a little harder, and with a more historical eye than the practitioners themselves? Is it not possible to see something a little more significant lurking amongst those “cocktails”; something almost imperceptible but, nonetheless, profound? Let us briefly imagine that this is so; that we have managed to coax that something out into a space of visibility: the multifactorial is coming back into vogue, and mixed cell-cultures are taking on elements of the original, but long since rejected Winogradskian culture, and allowing for the simultaneous and interactive growth of multiple pathogens. Suddenly the questions we are able to ask without, as yet, being able to answer, are transformed. With these subtle shifts in practical, everyday, seemingly innocuous technique, for instance, might we perhaps be teetering on the edge of an epistemological threshold in the medical microbiological sciences? In years to come, might the 2003 SARS outbreak stand as just one amongst a long and ever expanding list of infectious diseases in which singular aetiology reigned supreme? Or might we perhaps come to see it as the last of the great modern infectious diseases? More generally, might the reinvention and redevelopment of a multifactorial style of microbiological practice transform us all into Winogradskians as much as Kochians, heralding a new dawn for the interactive, multifactorial pathogen, a possibility that has been repressed in medical microbiology for over a century?

Notes

¹ René Dubos, *Mirage of Health: Utopias, Progress, and Biological Change*, (New Jersey: Rutgers University Press, 1959[1996]).

² *Ibid.*, 101.

³ *Ibid.*, 102.

⁴ *Ibid.*, 118.

⁵ *Ibid.*, 101. On the doctrine of specific aetiology and its importance to modern western medicine, see David Gordon, "Tenacious assumptions in western biomedicine", in *Biomedicine Examined*, eds., Margaret Lock, David Gordon (Dordrecht: Kluwer Academic, 1988). For more detailed histories of its emergence during the late nineteenth century, see K. Codell Carter, *The Rise of Causal Concepts of Disease* (Aldershot: Ashgate, 2003), 129–146; C. Barlow and P. Barlow, *Robert Koch* (Geneva: Heron Books, 1972), 241–269; Thomas Brock, *Robert Koch: a life in Medicine and Bacteriology* (London: Springer, Verlag, 1988).

⁶ Alan Hinman, Jeffrey Coplan, Walter Orenstein *et al.*, "Live or Inactivated Poliomyelitis Vaccine: An Analysis of Benefits and Risks", *American Journal of Public Health*, vol. 78, no. 3 (1988), 291–295.

⁷ William H. Stewart was not alone in this way of thinking. Around the same time Macfarlane Burnet was writing of how "one can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious disease as a significant factor in social life" (Burnet, *Natural History of Infectious Disease*, Cambridge: Cambridge University Press, 1962), p. 47). And, a little earlier, Henry Sigerist, felt able to suggest that "most of the infectious diseases . . . have now yielded up their secrets . . . Many illnesses . . . have been completely exterminated; others have been brought largely under control" (Sigerist, *The Great Doctors* (New York: Academic Press, 1933[1971]), 371).

⁸ On William H. Stewart's address to the state and territorial health officers, see Laurie Garrett, *The Coming Plague: Newly Emerging Diseases in a World out of Balance* (New York: Penguin), 33. Also useful for their accounts of this period of "biomedical optimism" are Mitchell Cohen, "Changing patterns of infectious disease", *Nature*, vol. 406 (2000), 762–767; and Andrew Cunningham, "A walk on the wild side – emerging wildlife diseases", *British Medical Journal*, vol. 331, no. 7527 (2005), 1214–1215.

⁹ "An Aristotelian philosophy of life", in the sense that the practical philosophies held to by medical practitioners like William H. Stewart tended to divide the world into two: on one side there was that which knows – the subject – and on the other was that which was known or perceived – the object. And this is "Aristotelian" because, as the philosopher A.N. Whitehead has noted, at its base this "great divide" is the result of a tacit adoption of Aristotle's notion of "primary substance": "Aristotle introduced the static fallacy by another concept which has infected all subsequent philosophy. He conceived primary substances as the static foundations which received the impress of qualification" (A.N. Whitehead, *Adventures of Ideas*, (New York: Free Press, 1933[1967]), 276). To think with Aristotle, then, is essentially to conceive of a ground or static base which comprises utter reality and which exists in complete isolation from the world of human perceptions and thoughts.

¹⁰ Dubos, *Mirage of Health*, 77.

¹¹ Dubos, *Mirage of Health*, 102 my emphasis.

¹² René Dubos, *Man, Medicine, and Environment* (Harmondsworth, England: Penguin Books, 1968), 106.

¹³ *Ibid.*, 108.

¹⁴ *Ibid.*, 109. And more generally, see René Dubos, *Louis Pasteur: Free Lance of Science* (London: Victor Gollancz Ltd., 1950); René Dubos, "Health and disease", *Journal of the American Medical Association*, vol. 174, no. 5 (1960), 505–507; René Dubos, "Pasteur's dilemma – the road not taken", *ASM News*, vol. 40 (1974), 703–709.

¹⁵ Steven Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge* (Berkeley: University of California Press, 1996), 57. Also see Charles Rosenberg, *The Care of Strangers* (Baltimore: John Hopkins University Press, 1987, 141) in which it is suggested that the doctrine "transform[ed] every aspect of medicine"; David Barnes ("Review of Spreading Germs", *Medical History*, vol. 47, no. 1 (2003), 115) makes the claim that it "forever chang[ed] the nature of medical knowledge".

¹⁶ This process of "normalisation" can be traced back at least as far as the late 1970s. See for example Russell A. Jones, *Self-fulfilling Prophecies* (New York: John Wiley & Sons, 1977), 214–215; Peter Conrad and Joseph Schneider, *Deviance and Medicalization: from badness to sickness* (New York: Temple University Press, 1992), 33; and Sarah Nettleton, *The Sociology of Health and Illness* (Cambridge: Polity, 2006), 2.

¹⁷ Lewis Kuller, "Relationship between acute and chronic disease epidemiology", *Yale Journal of Biology and Medicine*, vol. 60, no. 4 (1987), 364.

¹⁸ But see in particular, Maureen O'Malley, John Dupré, "Size doesn't matter: towards a more inclusive philosophy of biology", *Biology and Philosophy*, vol. 22, no. 2 (2007), 162.

¹⁹ Thomas Rivers, "Viruses and Koch's Postulates", *Journal of Bacteriology*, vol. 33, no. 1 (1937), 1–12.

²⁰ *Ibid.*, 4–5.

²¹ Jonathan Cohen and William Powderly, *Infectious Diseases Volume 1 (2nd edition)* (London: Mosby, 2006).

²² David Fredricks, "Diseases of unknown etiology: the role of infectious agents", in *Infectious Diseases*, eds. Cohen and Powderly.

²³ World Health Organisation, "WHO issues a global alert about cases of atypical pneumonia", URL (consulted 14 January 2010), available at: <http://www.who.int/mediacentre/news/releases/2003/pr22/en/>

²⁴ Klaus Stöhr, "A multicentre collaboration to investigate the cause of SARS", *Lancet*, vol. 361, no. 9370 (2003), 1730.

²⁵ World Health Organisation, "World Health Organisation issues emergency travel advisory", URL (consulted 14 January 2010), available at: http://www.who.int/csr/sars/archive/2003_03_15/en/

²⁶ *Ibid.*

²⁷ Thomas Ksiazek, Dean Erdman, Cynthia Goldsmith *et al.*, "A novel coronavirus associated with SARS", *New England Journal of Medicine*, 2003, 348(20).

²⁸ Dubos, "Mirage of health", 101.

²⁹ Bruno Latour, *Science in Action* (Cambridge, Mass.: Harvard University Press, 1987), 100.

³⁰ In comparison to Robert Koch, little has been written about the technical details of Sergei Winogradsky's work. But see Debra Bibel, *Microbial Musings: a History of Microbiology* (Belmont, Calif.: Star Publishing, 2001); Eric Kupferberg, "A field of great promise: soil bacteriology in America, 1900–1925", *Endeavour*, vol. 27, no. 1 (2003), 16–21; Maureen

O'Malley, " 'Everything is everywhere: but the environment selects': ubiquitous distribution and ecological determinism in microbial biogeography", *Studies in History and Philosophy of Biology and Biomedical Sciences*, vol. 39, no. 3 (2008), 314–325; G. Zavarzin, "Winogradsky and modern microbiology", *Microbiology*, vol. 75, no. 5 (2006), 510. Although Winogradsky is now often claimed as a "soil" or "general" microbiologist whilst Robert Koch is remembered as a pioneering "bacteriologist" or "medical microbiologist", these are all "after the event" categorisations. At the turn of the 19th century, the fertile fields and commons of the microbial world had not yet suffered their enclosures at the hands of various disciplines and sub-disciplines.

³¹ M. Penn, M. Dworkin, "Robert Koch and two visions of microbiology", *Bacteriological Reviews*, vol. 40, no. 2 (1976), 276–283.

³² *Ibid.*, 276.

³³ *Ibid.*

³⁴ *Ibid.*, 279–280 my emphasis.

³⁵ *Ibid.*, 280.

³⁶ *Ibid.*

³⁷ *Ibid.*

³⁸ *Ibid.*, 279–280 my emphasis.

³⁹ *Ibid.*, 280.

⁴⁰ *Ibid.*, 281.

⁴¹ Robert Koch, "Investigations into the etiology of traumatic infective diseases", in *Milestones in Microbiology*, ed. Thomas Brock (New York, Greenwood Press, [1880]1961), 97.

⁴² Perhaps the clearest exposition of the "hybrid" can be found in Latour's discussion of the ways in which debates about the unrestricted sale of guns in American tend to be structured. On one side, we find the slogan "guns kill people", and, on the other, the slogan "guns don't kill people; people kill people" ("On Technical Mediation: The Messenger Lectures on the Evolution of Civilization", *Cornell University, Institute of Economic Research, Working Papers Series*, 1993). But for Latour, it is more useful to conceive of the "person-gun". Rather than the "gun" or the "person" having an essence – either good, bad, or neutral – Latour's argument is that the "person-gun" is a hybrid entity, entailing new associations. In the process of their coming together, both person and gun become different. As Latour puts it, the mistake "is to start with essences, either those of subjects or those of objects. . . . Either you give too much to the gun or too much to the gun-holder. Neither the subject, nor the object, nor their goals are fixed for ever. We have to shift our attention to this unknown X, this hybrid which can truly be said to act" (*ibid.*, 6). In terms of the debate between Koch and Winogradsky, then, Winogradsky's "biotype" can usefully be conceived as a coming together of two (or more) separate pathogens that, in the very process of coming together, create a wholly new entity.

⁴³ Sergei Winogradsky, *Soil Microbiology: Problems and Methods* (Moscow, Akad: Nauk SSSR, 1952), 344 my emphasis.

⁴⁴ Penn and Dworkin, "Robert Koch", 277.

⁴⁵ In a sense, the medical microbiological theory of "multifactorality" is a practical, material version of Alfred North Whitehead's "processual" philosophy. In Whitehead's view, too many western philosophers had been led astray by the "evil" of Aristotelian notions of "substance" (A.N. Whitehead, *Process and Reality: An Essay in Cosmology* (New York: Free Press,

1978[1929]), 30). Nature/culture, object/subject, real/constructed: for Whitehead, these were the unhelpful, intractable dualisms that sprang up in their wake. But what Whitehead saw in life was not autonomy, separation and purity, but immersion, complexity and impurity. And if he subsequently came to refer to his own project as “the philosophy of organism . . . a recurrence to pre-Kantian modes of thought” (Ibid., xi) then perhaps it might be possible to characterise multifactoriality’s project as “the philosophy of the pathogen”. On Whitehead’s philosophy, also see Isabelle Stengers, “A constructivist reading of Process and Reality”, *Theory, Culture and Society*, vol. 24, no. 4 (2008), 1878–1884.

⁴⁶ This description of a culture as a “body outside of the body” is taken from Hannah Landecker, *Culturing Life: How Cells Became Technologies* (London, Harvard University Press, 2007), 107–139.

⁴⁷ Robert Koch, “Methods for the study of pathogenic organisms”, in *Milestones in Microbiology*, ed. Thomas Brock.

⁴⁸ Ibid., 102.

⁴⁹ Ibid., 104.

⁵⁰ Ibid., 106.

⁵¹ J. Collee and W. Marr, “Cultivation of bacteria” in *Practical Medical Microbiology*, eds., J. Collee, J. Duguid, A. Fraser, B. Marmion (New York, Longman, 1989), p. 123.

⁵² Ibid., 104

⁵³ Ibid.

⁵⁴ Ibid., 106.

⁵⁵ Ibid., 107.

⁵⁶ Ibid.

⁵⁷ Zavarzin, “Winogradsky and modern microbiology”, 510.

⁵⁸ Winogradsky, “Soil”, 783.

⁵⁹ Winogradsky, cited in S. Waksman, “Sergei Nikolaevitch Winogradsky, the story of a great bacteriologist”, *Soil Science*, vol. 62 (1946), 336.

⁶⁰ Winogradsky, “Soil”, 789.

⁶¹ Hans Schlegel, “Winogradsky discovered a new *Modus Vivendi*”, *Anaerobe*, vol. 2, no. 3 (1996), 67.

⁶² Winogradsky, “Soil”, 783.

⁶³ Ibid., 344, my emphasis.

⁶⁴ Ksiazek *et al.*, “Novel”, 1953.

⁶⁵ Ibid., 1961.

⁶⁶ On the notion of time as “crumpled” and “folded” rather than “linear”, see the philosopher Michel Serres’ comments in Bruno Latour and Michel Serres, *Conversations on Science, Culture and Time* (Michigan, Ann Arbor, 1995), 57–66.

⁶⁷ Ksiazek *et al.*, “Novel”, 1954.

⁶⁸ Geo. Brooks, Janet Butel, Stephen Morse *et al.*, eds., *Jawetz, Melnick and Adelberg’s Medical Microbiology (23rd edition)* (London, McGraw Hill, 2004).

⁶⁹ Ibid., 380–381.

⁷⁰ Ibid., 380. Also on this “purification process”, see P. Minor, “Concentration and purification of viruses”, in *Virus Culture: A Practical Approach*, ed. Alan Cann (Oxford, Oxford University Press, 1999); Gregory Storch, “Specimen collection guide”, in *Essentials of Diagnostic Virology*, ed. Gregory Storch (London, Churchill Livingstone, 2000).

⁷¹ Ibid., 381 my emphasis.

⁷² Ksiazek *et al.*, “Novel”, 1953.

⁷³ David Knipe and Peter Howley, eds., *Fields Virology* (5th edition) (London: Lippincott Williams and Wilkins, 2007).

⁷⁴ Storch, "Diagnostic virology", in Knipe and Howley, eds., *Fields*, 565–594.

⁷⁵ *Ibid.*, 566.

⁷⁶ *Ibid.*

⁷⁷ Ksiazek *et al.*, "Novel", 1954.

⁷⁸ WHO, "Sampling for severe acute respiratory syndrome diagnostic tests", URL (consulted 14 January 2010), available at <http://www.who.int/csr/sars/sampling/en/>

⁷⁹ *Ibid.*

⁸⁰ *Ibid.*

⁸¹ *Ibid.*, my emphasis.

⁸² Janet Butel, "General properties of viruses", in *Jawetz, Melnick and Adelberg's Medical Microbiology* (24th edition), eds., Geo Brooks, Janet Butel, Stephen Morse *et al.*, (London, McGraw Hill, 2007), 380.

⁸³ Tom Elliot, Tony Worthington, Husam Osman, Martin Gill, *Medical Microbiology and Infection* (Oxford, Blackwell, 2007), 127.

⁸⁴ WHO, "Sampling".

⁸⁵ Diane Leland and Christine Ginocchio, "Role of cell-culture for virus detection in the age of technology", *Clinical Microbiology Reviews*, vol. 20, no. 1 (2007), 50 my emphasis.

⁸⁶ Elliot *et al.*, *Medical*, 127 my emphasis.

⁸⁷ Leland and Ginocchio, "Role", 50 my emphasis. On this point also see Richard Slack, "Diagnostic procedures", in *Medical Microbiology*, eds., David Greenwood, Richard Slack, John Peuthere, Michael Barer (Edinburgh, Elsevier, 2007), 666–668; Betty Forbes, Daniel Sahn, Alice Weissfeld, eds., *Bailey and Scott's diagnostic microbiology* (St. Louis, Mosby Publishers, 2002).

⁸⁸ Ksiazek *et al.*, "Novel", 1954.

⁸⁹ Geo. Brooks, Janet Butel, Stephen Morse *et al.*, eds., *Jawetz, Melnick and Adelberg's Medical Microbiology* (24th edition) (London, McGraw Hill, 2007).

⁹⁰ Karen Carroll, "Principles of diagnostic medical microbiology", in Brooks *et al.*, eds., *Jawetz*, 725. Issues of preparation are addressed in greater detail in A. Cann, W. Irving, "Virus isolation", in A. Cann, ed., *Virus*; Storch, "Specimen"; Thomas Smith, "Specimen requirements: selection, collection, transport, and processing", in Steven Specter, Richard Hodinka, Stephen Young, eds., *Clinical Virology Manual* (3rd edition) (Washington, ASM Press, 2000); Danny Wiedbrauk, Sheryl Johnston, *Manual of Clinical Virology* (New York, Raven Press, 1993).

⁹¹ *Ibid.*, my emphasis.

⁹² Leland and Ginocchio, "Role", 50; and, for an understanding of the (very similar) processing guidelines in existence in other laboratories, see Florence Bursleson, Thomas Chambers, Danny Wiedbrauk, *Virology: A Laboratory Manual* (San Diego, Academic Press, 1992); Michael Forman and Alexandra Valsamakis, "Specimen collection, transport, and processing: virology", in Patrick Murray, Ellen Baron, James Jorgensen, Michael Pfaller, Robert Yolken, eds., *Manual of Clinical Microbiology* (8th edition) (Washington, ASM Press, 2003); and Smith, "Specimen".

⁹³ *Ibid.*

⁹⁴ Carroll, "Principles", 727–728.

⁹⁵ Latour, *Science in Action*; Harry Collins, *Changing Order* (London: Sage Publications, 1985).

⁹⁶ This reference to “constructivist science studies” is informed by a reading of the philosopher Annemarie Mol (*The Body Multiple: Ontology in Medical Practice* (Durham: Duke University Press, 2002), 33–44). The reference to “distribution” is a nod to her work on the distribution of possible realities in surgical treatment across multiple sites (see *Ibid.*, 108–114).

⁹⁷ Enteroviruses and vaccinia viruses, for example, are *known* to be harmed by ether. Thus, in cases where infection with either family of virus is *expected*, ether is not used in the preparation of samples. But of course, to talk of what is *known* and *expected*, is also to raise some rather interesting questions about where the line is drawn in medical microbiology between the *known* and the *unknown* and the *expected* and the *unexpected*. So read on . . .

⁹⁸ Smith, “Specimen”, 13.

⁹⁹ Forman and Valsamakis, “Specimen collection”, 1,228 my emphasis.

¹⁰⁰ Carroll, “Principles”, 727.

¹⁰¹ Butel, “General”, 380.

¹⁰² *Ibid.*

¹⁰³ Ksiazek *et al.*, “Novel”, 1957.

¹⁰⁴ Winogradsky, cited in Waksman, “Sergei”, 333.

¹⁰⁵ Winogradsky, “Soil”, 783.

¹⁰⁶ Dubos, *Mirage of Health*, 108–109.

¹⁰⁷ Elliot *et al.*, *Medical Microbiology*, 127 my emphasis.

¹⁰⁸ Steven Specter, Richard Hodinka, Danny Wiedbrauk, Stephen Young, “Diagnosis of viral infections”, in *Clinical virology*, eds., Douglas Richman, Richard Whitley, Frederick Hayden (Washington, ASM Press, 2002), 243.

¹⁰⁹ *Ibid.*

¹¹⁰ See the references in endnote 90, above.

¹¹¹ Storch, “Diagnostic virology”, 567. And as Storch (*Ibid.*, 568) also makes clear, “inadequate or improper specimen collection and transport accounts for the largest source of error in the accuracy of viral test results”.

¹¹² Leslie Collier and John Oxford, *Human Virology: a Text for Students of Medicine, Dentistry, and Microbiology* (Oxford, Oxford University Press, 2000), 244.

¹¹³ Specter *et al.*, “Diagnosis”, 244.

¹¹⁴ Storch, “Diagnostic”, 567.

¹¹⁵ Ksiazek *et al.*, “Novel”, 1955.

¹¹⁶ Butel, “General”, 727.

¹¹⁷ J. Kahn, “Newly discovered respiratory viruses: significance and implications”, *Current Opinion in Pharmacology*, vol. 7 (2007), 478.

¹¹⁸ Fredricks, “Diseases of unknown etiology”, in *Infectious Diseases*, eds. Cohen and Powderly, 95.

¹¹⁹ *Ibid.* For a more detailed discussion of the problem of the *unknown* in virological research, and the ways in which new molecular diagnostic techniques are beginning to reveal hitherto unknown pathogenic forms, see Martin Blaser, “Bacteria and diseases of unknown cause”, *Annals of Internal Medicine*, vol. 121 (1994), 144–145; T. Sloots, D. Whitley, S. Lambert, M. Nissan, “Emerging respiratory agents: new viruses for old diseases”, *Journal of Clinical Virology*, vol. 42, no. 3 (2008), 233–243; and Antonia Suau, Régis Bonnet, Malène Sutren, “Direct analysis of genes

encoding 16S rRNA from complex communities reveals many novel molecular species within the human gut", *Applied Environmental Microbiology*, vol. 65 (1999), 4799–4807.

¹²⁰ Koch, cited in Codell-Carter, *The Rise of Causal Concepts of Disease*, 137–138.

¹²¹ Patrick Collard, *The Development of Microbiology* (Cambridge, Cambridge University Press), 18.

¹²² Ksiazek *et al.*, "Novel", 1957.

¹²³ On the notion of time as "crumpled" and "folded" rather than "linear" and "flowing", see Serres' comments in Bruno Latour and Michel Serres, *Conversations on Science, Culture and Time* (Michigan: Ann Arbor, 1995), 57–66.

¹²⁴ Hacking, "Style"; and Hacking, "The self".

¹²⁵ Hacking, "The self", 29.

¹²⁶ *Ibid.*, 30 my emphasis.

¹²⁷ *Ibid.* my emphasis.

¹²⁸ *Ibid.*, 57–58.

¹²⁹ As O'Malley and Dupr (‐Size‐, 162 my emphasis) have noted, for instance: ‐ecological studies of microbes (historically not part of general ecology, but a subfield of microbiology) have been marginalized throughout most of the history of microbiology by the pure culture paradigm and the lack of effective alternative methods‐.

¹³⁰ Consider, for example, the story of how extensive epistemic work was undertaken in order to finally understand the ‐synergistic‐ interaction between hepatitis D virus and hepatitis B virus that causes certain cases of hepatitis (John Gerin, John Casey, Robert Purcell, ‐Hepatitis Delta Virus‐, in David Knipe and Peter Howley, eds., *Fields Virology* (4th edition) (London, Lippincott Williams and Wilkins, 2001).

¹³¹ Fredricks, ‐Diseases‐, 95.

¹³² Brian Mahy, Van ter Meulen, eds., *Topley & Wilson's Microbiology and Microbial Infections* (Vol. 2) (London, Hodder Arnold, 2005).

¹³³ Steven. Specter and Mauro Bendinelli, ‐The laboratory diagnosis of viral infections‐, in *Topley*, eds., Brian Mahy, Van ter Meulen, 1541.

¹³⁴ *Ibid.*

¹³⁵ *Ibid.*

¹³⁶ *Ibid.*, my emphasis.

¹³⁷ Leland and Ginocchio, ‐Role‐, 57 my emphasis.

¹³⁸ See for example Yung Huang, Scott Hite, Visa Duane, ‐Application of mixed cell lines for the detection of viruses from clinical specimens‐, *Clinical Microbiology Newsletter*, vol. 22, no. 12 (2000), 89–92; Kirsten St George, Navin Patel, ‐Rapid and sensitive detection of respiratory virus infections for directed antiviral treatment using R-mix cultures‐, *Journal of Clinical Virology*, vol. 24 (2002), 107–115.