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Constructing Scientific Knowledge: The Understanding of the Slow Virus, 1898-1976

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Abstract

Scrapie is the ovine form of the transmissible spongiform encephalopathies. The understanding of scrapie as a slow viral disease was developed through an international scientific dialogue during the first half of the twentieth century. British investigators used epidemiological and experimental observations to define its very long incubation period before the appearance of symptoms. This enabled French researchers to prove scrapie could be transmitted from sick to healthy animals and allowed them to define the etiological agent as an ultramicroscopic, filterable virus. Following this, an Icelandic scientist, Björn Sigurdsson, investigated two other ovine diseases characterized by unusually long periods between contracting the agent and actually developing symptoms of the illness. Because he was able to show the disease was actually present during this time, he reimagined the incubation period as one of latency with subclinical manifestations: the disease was simply progressing very slowly without obvious signs. Thus, Sigurdsson first articulated the concept of the slow viral infection to explain this new understanding of certain transmissible diseases. During the 1950s and 60s, researchers in New Guinea investigated the nature of an entirely new disease, kuru. They ultimately conceptualized it as a slow viral disease transmissible from one host to another. All of this research, taken together, illustrates the way twentieth century scientists worked to conceptualize the etiology of poorly understood diseases. Moreover, this decades-long scientific dialogue nicely illustrates how our understanding of, and

appreciation for, the scientific construction of biomedical knowledge complements the more commonly portrayed social construction of scientific knowledge.

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Introduction

In December 1984, dozens of cows in Britain began to stagger and die as the gray matter of their brains developed numerous holes and perforations. This process of tissue destruction, known as vacuolization, caused the cut surface of affected brain to resemble a sponge (or Swiss cheese). Hence, it was called ‘spongiform’ degeneration. This, of course, marked the beginning of the epidemic of mad-cow disease, known scientifically as bovine spongiform encephalopathy (BSE). Transmissible spongiform encephalopathies (TSE) are a class of diseases known to affect humans as well as various other animal species. The causative agent of TSEs can transmit the disease from infected to healthy animals and trigger this destructive spongiform degeneration of the brain. Within a decade, this disease of cattle had traversed the so-called ‘species barrier’ and begun to devastate the brains of over two hundred people who had eaten tainted beef. They developed variant Creutzfeldt-Jacob disease (vCJD), another form of TSE, which is triggered by the causative agent of BSE when it invades the human body. Variant CJD is so named because of its close similarity to a human disease first described in the 1920s by Drs. Creutzfeldt and Jacob, Creutzfeldt-Jacob disease (CJD). Though the two diseases are very similar, there are slight, but definite, ‘strain’ differences between these two manifestations of the disease in humans; one, for example, is transmitted by infected beef, and the other is thought to develop spontaneously.

Only two cases of mad-cow disease are known to have occurred in North America. Both of these obviously sick cows, however, were processed into meat and

entered the North American food chain in 2003 before anyone realized they were actually suffering from mad-cow disease. Some experts even considered that these findings meant the disease was endemic in North America. Nevertheless, there was no ensuing epidemic in Canada or the United States, and, after other countries began to embargo American beef, threatening a multi-billion dollar American product, stricter controls were introduced to restrict the processing of obviously sick, 'downer cattle.'[1] It is not known why there were no cases of transmission to humans, and the precise origin of mad cow disease is uncertain. The original epidemic in Britain was initially attributed to the use of contaminated sheep parts in the feed given to other animals.

Sheep are, in fact, subject to a TSE known as scrapie, but scrapie was of little concern, except to shepherds and flock owners, before its putative journey across the species barrier to cows. Additionally, various species of wild ungulates and captive felines living in British zoos also developed a spongiform encephalopathy in 1986, and the source was assumed to have been the same prepared food sources contaminated with infected sheep (or possibly bovine) parts that likely transmitted it to cattle.[2] Domestic cats in England also acquired a spongiform encephalopathy similar to scrapie in 1990; it

[1] See the foreword by Marion Nestle in, Maxime Schwartz, *How the Cows Turned Mad: Unlocking the Mysteries of Mad Cow Disease*, translated by Edward Schneider with a new foreword by Marion Nestle (Berkeley: University of California Press, 2003), IX-XVIII. Nestle is a molecular biologist and former professor of nutrition and public health at New York University, and her research focuses on both the scientific and social factors affecting the safety of food supplies.

[2] D. Carleton Gajdusek, "Infectious Amyloids: Subacute Spongiform Encephalopathies as Transmissible Cerebral Amyloidoses," in B.N. Fields *et al*, ed., *Fields Virology* (Philadelphia: Lippincott-Raven, 1996), 2884. See also, Bruce, M.E., Will, R.G., et al., "Transmissions to Mice Indicate that 'New Variant' CJD is caused by BSE Agent," *Nature* 389, issue 6650 (October 02, 1997): 489.

too, was linked to the ingestion of contaminated sheep, or bovine, additives to cat food.[3] Complicating this explanation, however, is evidence that it had appeared earlier in captive tigers, well before the mad-cow epidemic.[4] Even more intriguing is the much earlier appearance in 1947 of a spongiform encephalopathy in Wisconsin among captive mink, which had likely been fed downer cattle.[5] Along with the appearance in England among captive tigers before the mad-cow epidemic, this early appearance in mink in North America suggests that the disease has been present and more widespread, though unrecognized, for a far longer period of time. It may also indicate that virulence, and/or susceptibility, is very low, sporadic, or inconsistent and that the epidemic of mad-cow disease was an unusual, and unusually visible, aspect of a more common problem.

This thesis examines the conceptualization of the *slow virus* as an etiologic agent in animal and human disease over the course of the twentieth century, and it aims to do so from a solidly scientific point of view rather than from a more sociological viewpoint. Although the sociological methodology has become hugely influential since the last quarter of the twentieth century, it has not replaced the scientific methodology of historical research. Nor should it, because the two are complementary and not mutually exclusive. Both make important contributions to the history of science, and historians must retain and employ both. Though beyond the scope of this thesis, it should be noted that during the last two decades of the twentieth century, the causative agent of the transmissible spongiform encephalopathies was reimagined as an infectious protein, the

[3] Candace K. Mathiason et al, "Susceptibility of Domestic Cats to Chronic Wasting Disease," *Journal of Virology* 87, no. 4 (February 2013): 1947-1956.
[4] Gajdusek, "Infectious Amyloids," in *Fields Virology*, 2883.
[5] D. Burger and G.R. Hartsough, "Transmissible Encephalopathy of Mink," in *Slow, Latent, and Temperate Virus Infections* ed. D. Carleton Gajdusek, Clarence J. Gibbs, Jr. and Michael Alpers (Washington, US Public Health Service – NIH, 1965): 297-305.

prion. This immensely important idea completely replaced the idea of the slow virus and deserves its own explication. It has, in fact, superseded the slow virus in the current thinking about the etiology of these fascinating, if devastating, diseases.

Though uncommon, the transmissible spongiform encephalopathies cause an excruciatingly devitalizing disorder of dementia and incoordination that is believed to be invariably fatal in humans. Mad-cow disease gained worldwide attention by killing several hundred people. By the end of the century, that epidemic was brought under control by careful inspection and culling of infected sheep and cattle, but no treatment has ever been found. It is less well known that during the same time period, twice as many people died from the iatrogenic transmission of the most common form of human TSE: Creutzfeldt-Jacob disease.[6] No viral agent has been definitively identified in the usual sense of being cultured or visualized with electron microscopy. Based on experimental observations, various characteristics of the presumed organism have been proposed, but consensus, never mind unanimity, about the agent has been difficult to achieve. In fact, the scientific discourse concerning the infectious agent became confused and highly contentious as the focus shifted from a virus to an infectious protein, the prion, in the last decades of the twentieth century.[7]

The prion is a completely novel infectious entity with certain characteristics that even seem to contradict fundamental tenets of biology. There are still a few skeptics who doubt it actually causes the diseases and, for various reasons, prefer the older concept of

[6] About four hundred people acquired CJD (and died) during the last quarter of the twentieth century from contaminated neurosurgical instruments or implants, injections of contaminated human growth hormone, or corneal transplants.

[7] The term prion was coined in the late twentieth century as an *ad hoc* appellation for 'infectious protein;' the latter was itself a totally new concept within germ theory.

the slow virus. Despite being rare entities, the TSEs and prions have assumed more relevance as they increasingly appear to be related to other, much more common, diseases including Alzheimer's, multiple sclerosis, Lou Gehrig's disease, and others of poorly understood etiology. Strikingly, their occurrence also seems to be sporadic, infectious, and hereditary, which is unusual, to say the least. Uncertainties such as these, inevitably contribute to the initial scientific conceptualization of a disease and its etiology, as well as to how that conceptualization may change over time.

The story begins with the microscopic work of French scientists in the late nineteenth century followed by the epidemiological and experimental work of several British researchers. One of the latter provided a crucial clue allowing another group of French investigators to show the disease was the result of a transmissible agent, probably a virus. An Icelandic scientist studying ovine diseases then redefined the etiologic agent as a virus with somewhat novel characteristics. Crucial to this lengthy scientific endeavor was the dialogue carried on by different investigators in scientific journals. Indeed, these scientific journals provide the bulk of the primary source materials for this study, but it is also necessary to briefly consider how scientists interpret empirical evidence in order to create new knowledge about diseases and disease etiologies.

Chapter 1 briefly summarizes the development of ideas of contagion and the use of the term *virus* from ancient to modern times culminating in the way viruses were understood during the twentieth century. This background information is necessary because the thesis deals with the conceptualization of scrapie as a contagious (transmissible) disease and the evolution in thinking about the nature of the transmissible agent as a slow virus. It thus requires some understanding of the history of contagion and

infection prior to the nineteenth century. In doing so, the first chapter inevitably summarizes certain aspects of the conceptualization of the germ theory, which is often presented as taking shape rather abruptly over the course of several decades near the end of the nineteenth century. This compression of historical time is typical when seen in retrospect. The development of germ theory, however, was ultimately the product of a much longer period of scientific discourse and debate extending across centuries and international boundaries.

Because the thesis is ultimately focused on the development of the concept of a slow virus, chapter 2 examines the early history of virology and how late nineteenth-century scientists began to distinguish viruses from bacteria. It details the initially vague conceptualization of the virus, over the course of several decades and extending into the early twentieth century, as an entity distinct from bacteria but otherwise unseen and poorly characterized. Chapters 3 and 4 examine the scientific understanding of the first two diseases realized to be transmissible spongiform encephalopathies: scrapie and kuru.

Chapter 3 looks at the evolution of the understanding of scrapie and its etiology during the first half of the twentieth century. By the late 1960s, scrapie would be conceived of as a ‘slow viral infection’ caused by a ‘slow virus.’ But the slow virus was a concept that did not exist at the beginning of the twentieth century; its creation was the result of an international scientific discourse lasting decades. Examining how the understanding of scrapie developed from the late nineteenth century to the late 1960s, this essay aims to illuminate the importance of unfettered scientific discourse to the conceptualization of a disease entity, scrapie, and its causative agent, the slow virus. It focuses on the creation of new biomedical knowledge concerning scrapie that did not fit

into the usual paradigm of viral diseases developed at the beginning of the twentieth century.

Chapter 4 details the discovery and understanding of the human disease kuru, a process that also required years and much scientific discourse. It too was a discourse that extended across international and even disciplinary boundaries, involving scientists from diverse backgrounds including virologists, physicians, geneticists, and anthropologists. Ultimately, by the end of the 1970s, kuru was determined to be a slow viral disease: a TSE whose causative agent was conceptualized as a slow virus similar to that of scrapie. This scientific work earned the 1976 Nobel Prize in Physiology or Medicine for Daniel Carleton Gajdusek.

French molecular biologist, Maxime Schwartz has written an excellent history of the outbreak of bovine spongiform encephalopathy in Britain during the 1980s: *How the Cows Turned Mad: Unlocking the Mysteries of Mad Cow Disease*. His work includes a brief history of scrapie and kuru up to that point, but his main thesis deals with how and why the outbreak of mad-cow disease occurred and then spread across the species barrier to humans. His work is consistently scientific in methodology and pays scant attention to the more social aspects of the period. The work is an excellent introduction to the purely scientific aspects of the history but does not examine the period prior to 1985 in depth. It also does not discuss the philosophical implications of how the knowledge of spongiform encephalopathies was developed to that time. It is best in dealing with the development of knowledge after the timeframe of this thesis.

Canadian Jay Ingram, authored the monograph, *Fatal Flaws: How a Misfolded Protein Baffled Scientists and Changed the Way We Look at the Brain*, which looks at the history of our understanding of prions and is especially valuable for its focus on the actual cellular and molecular pathology that led to the development of the prion theory.[8] Having switched from microbiology to scientific journalism, Ingram is a genius at clearly explaining the complexities of cellular microbiology and protein chemistry. Although more concerned with the scientific work done after the timeline of this essay, Ingram does detail the work of Carleton Gajdusek, and is correct that the Nobel Laureate benefited immensely from the work of other researchers. But, in trying to apportion credit among the researchers, Ingram glosses over the more obvious importance of the scientific dialogue that was being developed by numerous individuals. More than the work of any one individual, it was this dialogue that was most important in elucidating and solving the problems surrounding scrapie and kuru.[9]

Historian of science, Warwick Anderson, has written the definitive scholarly account of kuru among the Fore peoples of New Guinea, *The Collectors of Lost Souls: Turning Kuru Scientists into Whitemen*. His work is a brilliant cultural, ethnographic, and anthropological analysis of the Fore and their interaction with the scientists striving to understand a disease new to science, if not to the Fore themselves. Anderson documents the modernization of a primitive people while simultaneously probing "the material

[8] Jay Ingram, *Fatal Flaws: How a Misfolded Protein Baffled Scientists and Changed the Way We Look at the Brain* (New Haven: Yale University Press, 2013).

[9] Ingram is also a bit cavalier in his approach to the philosophy of science, or as he puts it, "how science works." His recipe (page 30) involves mixing a few facts with some out-of-the-box thinking, a little luck, a dash of humor, *et voila*, "you've go new science." On the other hand, Ingram includes a fascinating and well-argued chapter (pages 32-42) discussing the controversies about the existence of cannibalism, including among the pre-Columbian Aztecs.

cultures of modern biomedical science [using] kuru brains [to] think more generally about the circulation of goods, the creation of value, the making of relationships, and the fashioning of identities in 'global' science."[10] Thus, Anderson adopts a markedly sociological approach to the creation of knowledge. This thesis, on the other hand, while using many of the same sources studied by Anderson, aims to understand how kuru was conceptualized scientifically and defined as a biomedical disease by different groups of scientific investigators, over the middle decades of the twentieth century.

The aim is not to present merely an internalist account of medical epistemology but rather to develop a synthesis of internalist and externalist threads for a more complete understanding. It is necessarily historical, because, the understanding of these diseases developed and changed over time and is best understood as a historical process with implications for the philosophical understanding of how the biomedical knowledge, more generally, may have evolved during the course of the twentieth century. Therefore, this thesis follows a historical and epistemological approach to the history of the understanding of these particular diseases and how, and why, conceptualizations of the diseases and their causation changed during the middle of the century.

In fact, it favors the approach of Eric Scerri who espouses an evolutionary epistemology and a belief that "science proceeds by almost imperceptible small steps in an evolutionary fashion not so much through the genius and brilliance of individual scientists but more by a process of trial and error, chance and sheer stumbling around."[11]

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[10] Warwick Anderson, *The Collectors of Lost Souls: Turning Kuru Scientists into Whitemen* (Baltimore: Johns Hopkins University Press, 2008), 1-6.
[11] Eric Scerri, *A Tale of Seven Scientists and a New Philosophy of Science* (Oxford: Oxford University Press, 2016), 4-5.

Scerri disagrees with Kuhn's belief in the advance of science through discontinuity and revolutionary change. Instead, Scerri conceives of science as an organic entity "in which scientific knowledge is viewed as one interconnected organism."[12] Moreover, scientific progress is an integral part of the organism, and the progress is gradual. The organism slowly evolves and progresses over time in response to various evolutionary forces, just as other living species evolve. Furthermore, just as evolution strives for the survival of a species, so evolutionary science leads to the survival of scientific knowledge.[13] Scientific progress is not abrupt or revolutionary in the Kuhnian sense. Furthermore, over long periods of time, scientific progress has depended almost as much on what scientists got wrong, at least initially.

Whether right or wrong, scientific observations and theories have all been part of this evolutionary process. If wrong, the organism has simply "put out a new limb, as it were, which turned out not to have any evolutionary advantage," but it might have had an advantage under different evolutionary circumstances or if subject to different evolutionary forces.[14] In nature, evolution seems to select for useful traits through natural selection. Similarly, in science, evolutionary epistemology selects the most productive, or useful, theories in order to better adapt itself to the natural world, and, like biological evolution, evolutionary epistemology and scientific progress "are neither right nor wrong."[15] Importantly, too, scientific progress should be seen as the result of small advances developed by numerous scientists, not just the famous scientists who are

[12] Scerri, *Seven Scientists and a New Philosophy of Science*, 10.
[13] Scerri, *Seven Scientists and a New Philosophy of Science*, 189.
[14] Scerri, *Seven Scientists and a New Philosophy of Science*, 22 and 168.
[15] Scerri, *Seven Scientists and a New Philosophy of Science*, 191.

wrongly credited with revolutionary changes.[16] Certainly, as will be evident in this history, the progress made in the understanding of scrapie and kuru was the work of numerous scientists in disparate locales, all joined in a productive scientific discourse. Or, as Scerri writes, "a multitude of individuals that frequently appear to be in competition with each other, while all the time furthering the common goal of a deeper understanding of nature."[17]

For most of the twentieth century, scientific progress seemed simple and straightforward. Scientists observed and investigated nature in order to obtain empirical evidence. From their findings, which they knew to be fallible, inferences were made. Experiments were then designed to test the validity of the inferences, and some were discarded while others were accepted as accurate. Using this methodological approach, scientists discovered aspects of the natural world from which explanations, or theories, were developed. These could be tested with more observations and experiments. Slowly, but progressively, some theories would be falsified and discarded; others, though, would be strengthened by further observation and experimentation. In this way, a reliable scientific method involving observation, analysis, experimentation, and the production of theoretical knowledge developed and became established as the scientific way in which to create knowledge about the natural world.

Over time, science has compiled an enviable series of important observations and theories constructing a complex, and often changing, appreciation of various aspects of the world, including health and disease. Scientists have, of course, been wrong,

[16] Scerri, *Seven Scientists and a New Philosophy of Science*, 36 and 64.
[17] Scerri, *Seven Scientists and a New Philosophy of Science*, 145.

sometimes repeatedly. Even when wrong, though, science often seems to have an admirable ability to correct itself and build on what has apparently been gotten right. Nonetheless, scientific research has resulted in some notably horrendous accomplishments such as nuclear and chemical weapons, as well as the villainous experiments of the Nazis and the Japanese Unit 731. Even so, most would agree that antibiotics, vaccines, and the elimination of smallpox constitute significant progress of great benefit to mankind.

Despite the undoubted false starts, missteps, and obvious errors, scientists continue to assemble more and more useful theories into an ever growing, productive, and apparently accurate, scientific understanding of nature. Moreover, the general acceptance of this portrait of the development of scientific knowledge remained stable until 1962 when Thomas Kuhn, a physicist, turned to the history of science for a better understanding of how scientists actually create new knowledge. His work, *The Structure of Scientific Revolutions*, was one of the most influential books of the last century and produced a dramatic transformation in how scholars think about science and scientific progress. For Kuhn, science has not progressed over time in an orderly fashion "by the accumulation of individual discoveries and inventions."[18] Instead, according to Kuhn, an "arbitrary element, compounded of personal and historical accident, is always a formative ingredient of the beliefs espoused by a given scientific community at a given time."[19] Moreover, the development of scientific knowledge has been "characterized by continual

[18] Thomas Kuhn, *The Structure of Scientific Revolutions*, 4th ed., 50th Anniversary Edition, with an Introductory Essay by Ian Hacking (Chicago: University of Chicago Press, 2012), 2.
[19] Kuhn, *Structure of Scientific Revolutions*, 4.

competition between a number of distinct views of nature … each compatible with, the dictates of scientific observation and method."[20]

In this essay, I would like to substitute words, such as 'discourse,' 'dialogue,' or 'debate,' for the word 'competition' in the above quote. The thesis of this essay is that free and unfettered discourse and debate are fundamental and necessary to the scientific construction of knowledge about diseases affecting humans and animals. This is not to argue that there was no competition. On the contrary, the debates often reflected competitive, sometimes even contentious, exchanges among researchers trying to find their way through confusing thickets of empirical evidence. However, the important aspect is not the shared or competing beliefs but the discursive dialectic constantly modifying investigators' beliefs and forcing the reexamination of empirical evidence and the reevaluation of older theories. This essay also reveals evidence of incidents involving Kuhn's 'arbitrary element, compounded of personal and historical accident.'

Kuhn argued that the conceptualization of a scientific problem leads to the creation of a paradigm within which scientific research is carried out. He maintained that when a paradigm is established (such as the germ theory) scientists working within that paradigm do not question it. They do not try to prove or disprove the paradigm itself; it is simply accepted as correct, and any evidence that seems to challenge the paradigm is overlooked, ignored, or pushed to the side.[21] Obviously, then, the paradigm exerts a profound influence on investigators. Moreover, because the prescriptive norms of scientific research lead to the conceptualization of a disease and the creation of a disease

[20] Kuhn, *Structure of Scientific Revolutions*, 4 (italics added).
[21] Kuhn, *Structure of Scientific Revolutions*, 23-51.

paradigm, these norms assume great importance to the accuracy of scientific results. Furthermore, how science conceives of a disease and its etiology is important, since it often governs how research is funded and how diseases continue to be investigated.

In fact, the history of medicine reveals that our understanding of various diseases has changed, sometimes dramatically, over time. Even the recent past has seen startling changes in the conceptualization of important and common diseases, such as peptic ulcer disease and cervical cancer. Part of the reason for this lies in the inferential problem of underdetermination that asserts the validity of more than one explanation for the same empirical data. That is, essentially any set of data may reasonably be interpreted in several different ways that are consistent with the data but inconsistent with each other.[22] As pointed out by philosopher of science, Kyle Stanford, the problem of underdetermination has often been exacerbated by scientists' inability to even conceive of certain explanations: "the history of science shows that we have repeatedly failed to conceive of (and therefore consider) alternatives to our best theories that were both well confirmed by the evidence available at the time and sufficiently plausible as to be later accepted by actual scientific communities."[23]

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[22] For example, it was long known that cervical cancer was much less prevalent among nuns. This suggested that cervical cancer was somehow related to the hormonal changes of pregnancy, which is rare among nuns. Equally, it could suggest that cervical cancer is the result of a sexually transmitted disease (also rare among nuns), such as human papilloma virus. The latter theory is now commonly accepted.

[23] P. Kyle Stanford, *Exceeding Our Grasp: Science, History, and the Problem of Unconceived Alternatives* (Oxford: Oxford University Press, 2006), 29. Though Stanford does not reference it, Kuhn did acknowledge this problem: "Philosophers of science have repeatedly demonstrated that more than one theoretical construction can always be placed upon a given collection of data;" see Kuhn, *Structure*, 76. Kuhn simply does not emphasize and develop this aspect of the problem the way Stanford does. Kuhn simply mentions it in passing.

Yet another difficulty arises from the notion of theory-laden observation: researchers are burdened with, and biased by, the predetermined notions of the paradigm within which they work. According to Kuhn, researchers may actually fail to see (to visually apprehend) evidence contrary to the expectations of a paradigm. Consequently, learning how scientists have correctly, or incorrectly, conceptualized disease in the past may help us appreciate and acknowledge where, and how, science can be misled. Many would contend that such an understanding is of more immediate and everyday importance within the medical sciences than it is, for example, in more esoteric subjects such as particle physics.

This thesis, then, addresses the question of how and why the conceptualization of the transmissible encephalopathies developed over the course of the first two thirds of the twentieth century. It is an attempt to understand the scientific discourse that led to new biomedical knowledge concerning the etiology of the transmissible spongiform encephalopathies in animals and humans. It aims to illuminate the way free and unfettered scientific debate led to the scientific construction of knowledge about slow viral infections and the scientific conceptualization of the slow virus as the etiologic agent of certain diseases. While this thesis examines the scientific construction of biomedical knowledge, the more sociological aspects affecting the construction of this same biomedical knowledge have been superbly examined in the aptly titled, *The Social Construction of Disease: From Scrapie to Prion*, by Kiheung Kim.[24]

[24] Kiheung Kim, *The Social Construction of Disease: From Scrapie to Prion* (New York: Routledge, 2007).

The social construction of scientific knowledge is based on the belief that all knowledge of the natural world is contingent on human understanding. Because scientists construct their understanding of the natural world, there can be no certainty that any objective reality exists. As Kim says, "what a certain disease 'is' is entirely dependent on the way people routinely act in relation to the disease."[25] Unfortunately, however, there is a "bewildering variety of conceptions of social constructivism [causing] confusion in the process of arriving at an agreed definition of what it is, much less an understanding of the significance of its implications for research activity."[26] Kim's work investigates the social circumstances and the institutional settings in which scientific work is done. For example, he is rightly concerned with the socio-economic importance of the wool industry in Britain to the early understanding of scrapie. But, while this is a good explanation for why research was undertaken, it does not really explain the research itself. Likewise, while an understanding of the institutions funding research is useful to our historical understanding of the research process, it is less instrumental in understanding the scientific aspects of the scientists' work.[27]

The social construction of knowledge differs significantly from scientific realism. Realism posits a natural world existing independently of any human understanding of it. Importantly, scientific realism proposes that scientific "truths are more dependent upon the natural world than upon the people who articulate them: there is a way that the world is, and it is possible to discover and represent it reasonably accurately."[28] Scientific

[25] Kim, *The Social Construction of Disease: From Scrapie to Prion*, 6.
[26] Kim, *The Social Construction of Disease: From Scrapie to Prion*, 5.
[27] Kim, *The Social Construction of Disease: From Scrapie to Prion*, 4-17.
[28] Sergio Sismondo, *An Introduction to Science and Technology Studies*, 2nd ed. (Oxford: Blackwell Publishing, 2010), 58.

realists, for example, believe that viruses are real entities completely independent of the human mind. Realists know that our present understanding of viruses is likely incomplete and will almost certainly undergo revision, but they believe viruses are real entities that can be seen with electron microscopy and were discovered, not contrived by scientists.

Certainly, scientific realists concede that external social factors, such as the beliefs and proclivities of women's advocacy groups may very well influence the scientific interpretation of breast cancer. However, many realists would argue that it is poor science that is being determined by this social construction of knowledge, because it loses sight of the internal, scientific norms that should define such research. By way of example, the game of chess is played and tournaments are sponsored for many different reasons, but these factors are external to the game itself. A particular game of chess is determined by internal rules governing how pieces move, threaten, and capture other pieces, and, it is these internal factors that determine the course and results of a game. One cannot understand a particular game without reference to these internal norms of chess. In the same way, one cannot understand the construction of scientific knowledge without reference to the internal norms of scientific research.

This essay takes a complementary approach to that of Kim and looks at the more internal, scientific aspects of how biomedical knowledge was developed. Both approaches yield valuable information and insights; they are not necessarily antagonistic or mutually exclusive. Kim, for example, also mentions the problem of underdetermination, but he suggests that the solution to this problem lies in a better

understanding of external social factors.[29] This essay, however, shows, at least with respect to the understanding of scrapie, that the problem of underdetermination required more scientific information. It required more observational data to narrow down the numerous possible, but underdetermined, explanations, and it required more theoretical speculation and more scientific discourse to articulate otherwise unconceived alternatives.

[29] Kim, *The Social Construction of Disease: From Scrapie to Prion*, 6.

Chapter 1

The Evolving Conception of Contagion and Infectious Diseases Before 1898

The ancient historian, Thucydides, described an epidemic disease spreading from person to person, during the second year of the Peloponnesian War (430 BCE). The citizens of Athens were bottled up in their city by the besieging army of Sparta, when "the plague first broke out among the Athenians."[30] Several times, Thucydides alludes to the apparent contagious spread of the plague: "mortality among the doctors was the highest of all, since they came more frequently in contact with the sick," and those "who did visit the sick, … lost their own lives."[31] Moreover, as "people were afraid to visit the sick," it is reasonable to assume that the public must have recognized it as somehow contagious.[32]

Thus, contagion was at least recognized, if not well understood in fifth century Greece. It was conflated with the way Greeks conceived of the spread of religious pollution through a community. In *Oedipus the King*, Sophocles depicted the corruption of impious behavior spreading within a society. The impiety is contagious and spreads through a community as a stain spreads through cloth. Just as Thucydides accepted, without comment, the spread of plague among people, Sophocles also accepted the

[30] Thucydides, *The Peloponnesian War* [Book II, Chapter 47], trans. Rex Warner (London: Penguin Books, 1954), 151.
[31] Thucydides, *Peloponnesian War* [II: 47,51], 152 and 154.
[32] Thucydides, *Peloponnesian War* [II: 51], 154.

contagious nature of sacrilege that could spread throughout a community. There was nothing revelatory about this observation for either ancient author; there is no suggestion that either situation would have been considered unusual in the ancient world.

The origins of the Athenian plague were, and remain, unknown. Thucydides, though, suggested it arrived from southern Egypt or Ethiopia, possibly carried to Greece on trading ships, because it first began in the port city of Piraeus. Though foul air and insalubrious winds were thought to provoke disease, transmission of the plague on trading vessels suggests some sort of agent more tangible than bad air. Moreover, modern attempts to find a rudimentary understanding of germ theory usually go back to Anaxagoras of Clazomenae (circa 500 – 428 BCE). An Ionian philosopher, Anaxagoras believed that seeds gave rise to the natural world. He mentioned "seeds" in two surviving fragments, and philosopher Richard McKirahan argues these are "microscopic particles … which are too small to be seen," and "have the same structure as the macroscopic objects."[33] Because they have the same structure as visible objects, these seeds could be either animate or inanimate objects.

McKirahan believes that Anaxagoras knew our senses are fallible and may not function below a certain threshold: "It is not that they [our senses] misreport what is the case, but that they may fail to report it."[34] Of the extant fragments from Anaxagoras' works, two stand out: "Because of their [the senses'] feebleness we are unable to discern the truth;" and "Appearances are a sight of the unseen."[35] Anaxagoras seems to have

[33] Richard D. McKirahan, *Philosophy Before Socrates: An Introduction with Texts and Commentary*, 2nd ed. (Indianapolis: Hackett Publishing Company, 2010), 202.
[34] McKirahan, *Philosophy Before Socrates*, 228.
[35] Quoted, critiqued, and analyzed in McKirahan, *Philosophy Before Socrates*, 193-229.

been trying to make sense of the unstable foundations of our knowledge of the natural world that we gather through our imperfect senses.[36] Moreover, the second fragment may be translated slightly differently as: "Phenomena are a vision of what is not manifest."[37] This alternate reading suggests the belief that we may legitimately and usefully make inferences about the invisible, microscopic world of seeds via analogous reasoning from those aspects of the natural world that we can see and otherwise perceive.[38]

In about 440-430 BCE, Leucippus and his student Democritus began to conceive of the natural world as composed of tiny, indivisible atoms that ultimately made up all objects and beings.[39] The most important of the ancient thinkers to adhere to the theories of Leucippus and Democritus was Epicurus (341-271 BCE), who developed an enduring school of ethics based on the materialism inherent in atomic theory and was very influential among Roman philosophers. The Roman writer Lucretius, for example, would invoke the ideas of Epicurus and atomist philosophy to create a novel explanation of how contagious diseases could be spread by these atoms or seeds.[40] Building on the ideas of atomism, Lucretius stressed the invisible particulate nature of seeds of disease and created an intellectual alternative to the idea of contagions that spread like heretical ideas or religious pollution through a community.

These ancient thinkers created a philosophical dialogue in which they tried to determine what and how various elements came together and in what combinations to

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[36] G.E.R. Lloyd, *Early Greek Science: Thales to Aristotle* (New York: W.W. Norton, 1970), 43.
[37] McKirahan, *Philosophy Before Socrates*, 228.
[38] Lloyd, *Early Greek Science: Thales to Aristotle*, 43.
[39] McKirahan, *Philosophy Before Socrates*, 303-342.
[40] Vivian Nutton, *Ancient Medicine*, 2nd ed. (London: Routledge, 2013), 149.

form the natural world. This, of course, included humans themselves, and much of the social thinking of the time was focused on the body politic within the different Greek city-states, trying to understand how societies functioned best and how, or why, they broke down into political disorder. Greeks debated issues concerning the proper constitution of, and balance of power within, a community in order to achieve harmony and order within the city-state.[41] This likely led medical thinkers to analogize the individual human body to the body politic, leading, in turn, to their belief that human illness was a constitutional disorder determined by an inadequate, or unbalanced, combination of elements within the human body.[42] Beginning with the teachings of Hippocrates, succeeding medical writers carried on a centuries-long discussion of health and disease, which developed into the Hippocratic Corpus.[43] Their efforts were mostly focused on the development of a humoral theory of disease that ascribed causation to an imbalance of the body's four humors, and they particularly rejected notions of divine causation of disease.

The treatise, *Nature of Man*, presented the elements of the humoral theory, and there has been considerable scholarly speculation, based on comments in Aristotle's writing, that the treatise was written by Hippocrates' son-in-law, Polybus. The author, whoever he was, argued,

> … blood, phlegm, yellow bile and black bile: these make up the nature of his body, and through these he feels pain or enjoys health … he enjoys the most

[41] Lloyd, *Early Greek Science: Thales to Aristotle*, 12-15.
[42] Nutton, *Ancient Medicine*, 46.
[43] The works usually attributed to Hippocrates were actually written by his successors over several centuries and collected under his name in the great library at Alexandria.

> perfect health when these elements are duly proportioned to one another in respect of compounding, power and bulk and when they are perfectly mingled.[44]

The humoral theory proposed that an internal imbalance of one or more of the body's humors caused different illnesses, and this precluded, at least among Greek writers, any idea of external seeds of disease causation. Nevertheless, the author of *Nature of Man* left the door open to some form of external causation when he postulated two categories of causation: lifestyle and the air men breathe. Discussing the appearance of the same disease among numerous people simultaneously, he argued "the cause must be ascribed to something common to all and which they all use; in other words to what they all breathe."[45] In the treatise, *Breaths*, the author clearly believes that "diseases are all the offspring of air."[46] He goes on to state that "whenever the air has been infected with such pollutions as are hostile to the human race, then men fall sick," and he uses the Greek word *miasma* (μιασμα) to indicate these pollutions.[47]

Greek medical writers did not develop a conception of contagion that opposed, or even complemented, the dominant concept of humoral imbalance.[48] They did not believe that epidemic diseases, for example, were transmitted by contact with sick individuals; rather it was the air they exhaled. Moreover, treatment was limited to the avoidance of the cause: the polluted air, or the *miasma*. The predominant doctrine of ancient medical

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[44] Hippocrates, *Nature of Man*, in *Hippocrates*, vol. IV of Loeb Classical Library, trans. W.H.S. Jones, (Cambridge: Harvard University Press, 1931), IX: 11.
[45] Hippocrates, *Nature of Man*, IX: 25.
[46] Hippocrates, *Breaths,* in *Hippocrates*, vol. II of Loeb Classical Library, trans. W.H.S. Jones, (Cambridge: Harvard University Press, 1923), V: 233.
[47] Hippocrates, *Breaths*, VI: 235. Despite the Hippocratic focus on natural causation, in contrast to divine causation, a strong tradition of religious healing did exist in ancient Greece that paralleled the rapidly developing secular and naturalistic tradition.
[48] Vivian Nutton, "To Kill or Not to Kill? Caelius Aurelianus on Contagion," in *Text and Tradition: Studies in Ancient Medicine and its Transmission – Presented to Jutta Kollesch*, ed. Klaus-Dietrich Fischer *et al*. (Leiden: Brill, 1998), 233-242.

thought emphasized the miasmatic theory developed by the Hippocratic author of *Breaths,* and this paradigm would remain the common belief in western medicine for several millennia. Even so, some Roman authors would later speculate on the transmission of minute seeds of disease through the air.

Recall that the Roman Epicurean philosopher, Titus Lucretius Carus (99 BCE-55 BCE), was a follower of the atomistic theory of Leucippus and Democritus; speculating on the existence of apparently invisible seeds, Lucretius proposed, "there are many seeds of things which support our life."[49] Having established the necessity of these to the support of human life, he immediately suggested that because there are seeds that are beneficial to mankind, "there must be many flying about which make for disease and death."[50] His idea of seeds likely derived from the work of Anaxagoras and the elemental, but invisible, seeds the latter had posited centuries earlier. Moreover, just as Anaxagoras seemed to reason that we could legitimately infer what is unseen from what that which is visible, Lucretius infers that, if there are beneficial seeds, there must also be harmful seeds, that is, seeds of disease.

On the other hand, Lucretius also says, "the air becomes diseased."[51] The very air itself seemingly becomes contagious and disease may descend from above or "may rise from the earth itself, when through damp it has become putrescent."[52] Thus, one finds both the idea of individual, particulate entities causing disease and the idea that rotting matter infects the air creating pestilential winds. Even while advocating his theory of

[49] Lucretius, *On the Nature of Things,* book VI: 1094-5, in Loeb Classical Library, trans. W.H.D Rouse (Cambridge: Harvard University Press, 1975), 575.
[50] Lucretius, *On the Nature of Things,* VI: 1095-1097, Loeb Classical Library, 575.
[51] Lucretius, *On the Nature of Things,* VI: 1099, Loeb Classical Library, 575.
[52] Lucretius, *On the Nature of Things,* VI: 1100-1101, Loeb Classical Library, 575.

seeds of disease, Lucretius adheres to the miasmatic theory. It is difficult to know whether he thought of contagion as the result of seeds carried by the wind or whether he thought the air itself was infectious. Or, perhaps he was unable to draw a clear distinction between these concepts. For example, he obviously recognized the difficulty of expressing such new ideas in a language not already adapted to them,

> … it is difficult to make clear the dark discoveries of the Greeks in Latin verses, especially since we have often to employ new words because of the poverty of the language and the novelty of the matters.[53]

Nevertheless, he certainly developed some conception of minute, invisible airborne particles which he called *semina vitalia* and which he associated with *contagium*.

Even the great Greek physician and humoral theorist Galen of Pergamon (129 CE – 200 CE) flirted briefly with the idea of 'seeds of contagion.' Doing so, he emphasized three things: "that the object posited is a living entity; that it is in origin very small; and that it contains within itself the potentiality for growth."[54] Given the emphasis on these three characteristics, such a theory almost certainly contains the rudiments of an ontological view of disease as an external entity that invades the human body. However, Galen never developed this flirtation into any sort of coherent theory. He never abandoned the humoral theory of disease. Indeed, Galen's fundamental belief in, and elaboration of, humoral theory was his great legacy to the medieval world. Historian Oswei Temkin has shown how Galen's thought was transmitted to medieval Europe as, what Temkin calls, Galenism. Medieval Galenism thoroughly rejected an ontological

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[53] Lucretius, *On the Nature of Things*, I: 136-139, Loeb Classical Library, 15.
[54] Vivian Nutton, "The Seeds of Disease: An Explanation of Contagion and Infection from the Greeks to the Renaissance," *Medical History* vol. 27, no. 1 (January 1983): 1-34, 3. Though Greek by birth, Galen lived and practiced in Rome during the 2nd century CE and was probably a Roman citizen.

view of diseases in favor of an internal humoral imbalance as embodied in the Hippocratic humoral theory of disease causation.[55] Just as Galen was a Greek physician who wrote and thought in Greek but practiced in Rome and even attended the Roman emperor, the word *virus* has both Greek and Latin roots.

The English word, virus, is ultimately derived from the Greek word, *iòs* through the Latin word *vīrus*. The classical use of the term suggested a poisonous substance, usually a fluid or liquid, such as the venom of a *viper* or the saliva of a rabid animal. The Roman author, Aulus Cornelius Celsus (25 BCE – 50 CE), addressed the bites of serpents and rabid dogs. In the first instance, he used the Latin word, *venenum*, for the poison, or venom, of a serpent. For the poisonous quality of rabid saliva, he used the Latin word, *virus*.[56] His use of different words may have been an effort to distinguish between the habitually poisonous secretions of the serpent and the unusually poisonous saliva of a rabid dog. However, one cannot read anything concerning the modern use of the term, virus, into ancient usage. Only gradually and over centuries did the term, virus, began to embody several ideas. It could mean the purulent discharge of an infected wound or ulcer; a substance produced within the body by an infectious disease; or essentially any disease-causing agent.

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[55] Oswei Temkin, *Galenism: The Rise and Fall of a Medical* Philosophy (Ithaca: Cornell University Press, 1973): 93-94, 134-136, 154-156. Temkin's brief sketch of Galen's physiology on pages 154-156 is admittedly simplistic, but it neatly summarizes the essential physiological underpinnings of medieval Galenism.

[56] Celsus, *On Medicine*, V: 27,1B-3C, vol. II in Loeb Classical Library, trans. W.G. Spencer, (Cambridge: Harvard University Press, 1938), 110-115.

Both virus and miasma infected humans by means of an invisible substance referred to as *contagium* by Latin authors.[57] Contagium, however, was (and remains) a flexible term implying more than simply the spread of disease. Recall, for example, that in the ancient world, *contagium* could also refer to the spread of sacrilege within a community. Likewise, it could suggest the bleeding of dye from one fabric into another or the spread of a liquid stain through cloth. In some cases, these poisons were visible, as in the case of dyes, stains, or the foaming saliva of rabid dogs. In other cases, however, the contagium was more insidious, like the foul smelling, though usually invisible, miasma that also caused diseases in humans.

The concept of contagion remained poorly defined during the medieval period of western history and mostly emphasized miasmatic causation. The Paris medical faculty, for example, wrote a learned analysis of the causes of the Black Death of 1348 ascribing the distant cause to a malign conjunction of planets,

> In 1345, at one hour after noon on 20 March, there was a major conjunction of three planets in Aquarius. This conjunction, along with other earlier conjunctions and eclipses, by causing deadly corruption of the air round us, signifies mortality and famine.[58]

In order to explain the more proximate cause of the pestilence, however, the faculty invoked the basic ideas of the miasmatic theory of causation: air corrupted by foul vapors emanating usually from decaying organic matter in the ground,

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[57] Alfred Grafe, *A History of Experimental Virology*, trans. Elvira Reckendorf (Berlin: Springer-Verlag, 1991), 1-5. It should be noted, however, that the eminent classicist, Vivian Nutton, also uses *virus* to mean 'harmful stench.' See his article (cited above), "The Seeds of Disease: An Explanation of Contagion and Infection from the Greeks to the Renaissance," *Med. Hist.* vol. 27 (1983): 11.

[58] Anonymous, "The Report of the Paris medical faculty," in *The Black Death*, trans. and ed. Rosemary Horrox (Manchester: University of Manchester Press, 1994), 159.

> What happened was that the many vapours which had been corrupted at the time of the conjunction were drawn up from the earth and water, and were then mixed with the air and spread abroad by frequent gusts of wind.[59]

This is usually considered to have been "the most authoritative contemporary statement of the nature of the plague" and its causation.[60] Its explanation of the proximate cause of the plague closely followed the miasmatic theory first articulated in the Hippocratic treatise, *Nature of Man*, and though other authors invoked various religious and secular causes, the idea of seeds of infection was notably absent.

During the medieval period, there was very little conscious consideration of particulate pathogenic matter, and this should not be surprising for three reasons. First, the classical theory of particulate seeds of infection did not feature in the standard medical writings they had inherited from the classical world. Galen's flirtation with 'seeds of infection' was fleeting. In reality he was a staunch humoralist, and this was the dogma he bequeathed to medieval Europe. Second, there was no way medieval scholars could comprehend, let alone elaborate on, the existence of invisible particulate matter. They could not see it and could not know of its existence. Finally, there was little or no medieval dialogue or debate about disease causation as there had been, for example, among the various ancient authors who had presented, discussed, and debated different theories and conceptions of disease. Such discourse had been largely suppressed by the widespread and uniform adherence to Galenism, which was solidly based on humoral theory.

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[59] Anon., "Report of the Paris faculty," in *The Black Death*, 161.
[60] Rosemary Horrox, *The Black Death* (Manchester: University of Manchester, 1994), 158.

This is not to say that medieval Europeans did not recognize leprosy, for example, as a transmissible disease; on the contrary, like ancient peoples, medieval peoples considered lepers to be contagious. Lepers were isolated from society and carried bells to warn others of approaching danger. Even so, most medieval physicians and scholars adhered to humoral medicine, and the reliance of medieval medicine on Galenic theory discouraged the conception of disease as an entity independent of the body's own humoral balance. Rather than being spread by external particulate matter, leprosy was thought to be spread by the noxious emanations arising from the lepers themselves. These emanations disrupted the humoral balance of anyone unfortunate enough to inhale them. It was not until the Renaissance that an ontological view of disease began to be reimagined perhaps partly out of the work of Lucretius and partly by the appearance of syphilis. Emerging shortly after Columbus' voyages of discovery to the New World, syphilis was quickly recognized as a venereal disease. Moreover, it was obviously contagious, and, partly because of the location of the initial lesions on the genitalia, it was easily understood to be transmitted through sexual intercourse. It was not transmitted by bad air, and it did not fit well into the humoral conception of disease.

The literary work of the Veronese physician, poet, and logician, Girolamo Fracastoro (ca. 1478-1553) led to calling the new venereal disease 'syphilis,' and his scholarly work created the outlines of a more modern conception of contagious matter and its spread. In 1546, Fracastoro published an erudite prose study concerning the etiology of contagious diseases in which he defined contagion as the result of direct or indirect contagion with 'seedlets of contagion' (*seminaria contagionis*), which produce a

disorder "originally caused by infection of the imperceptible particles."[61] Moreover, Fracastoro notes that "contagion is an infection that passes from one thing to another," and the imperceptible particles of contagion can cause disease by direct contact, through transmission by fomites, and at considerable distances.[62] Fracastoro is particularly perceptive concerning the transmission of infection by fomites:

> Things that have been touched by persons suffering from phthisis [consumption] or the plague are really amazing examples of this. I have often observed that in them this virus has been preserved for two or three years.[63]

He also notes that these infectious particles reproduce themselves "and at the same time procreate other germs precisely similar to themselves as progeny, which, when carried to another object transmit the contagion to it."[64]

Historian of ancient medicine, Vivian Nutton, argues that historians have frequently divined the origins of the 19th century germ theory in *De Contagione* and that Fracastoro's ideas were widely accepted within a decade of its publication. Lise Wilkinson also opines, "Fracastoro's fame rests primarily and deservedly, on his

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[61] Hieronymi Fracastoro, *De Contagione et Contagiosis Morbis et Eorum Curatione, Libri III*, trans. and notes by Wilmer Cave Wright (New York: G.P. Putnam's Sons; 1930), 5 (italics in the original translation). See also, Vivian Nutton, "The Reception of Fracastoro's Theory of Contagion: The Seed That Fell among Thorns?" *Osiris* vol. 6 (1990): 196-234.

[62] Fracastoro, *De Contagione*, 3 and 7-21.

[63] Fracastoro, *De Contagione*, 13. It is likely that Fracastoro used the term plague in a generic sense (probably including such epidemic diseases such as smallpox) rather than the narrow sense of the disease known to his contemporaries as the Great Mortality (today's bubonic plague).

[64] Fracastoro, *De Contagione*, 57. To be fair, while these quotes give a good sense of his efforts to develop an ontological theory of disease transmission based on infectious seeds, they tend to obscure the many of the inconsistencies in his writing.

formulation of the concept of contagion."[65] Nevertheless, without the ability to visualize and empirically verify the hypothetical 'seeds' there was no reason for his contemporaries to consider his thesis as anything more than simply another metaphor similar to others such as, putrefaction, occult poison, morbid excretion, or pestilent vapors by which medieval and Renaissance adherents to Galenic ideas had traditionally explained what made miasmas contagious.[66] Indeed, Fracastoro does not clearly distinguish between the concepts of putrefaction, morbid excretions, and pestilential vapors.

Fracastoro's work was typical of the humanist traditions of learning that preceded the mid-nineteenth century emphasis on the empirical evidence provided by laboratory science. He developed an idea enunciated in the works of classical authors even though he could not see many fomites or any seeds of contagion. He certainly could not investigate their characteristics. Nevertheless, reinvigorating the metaphor of seeds of infection gave renewed credence to the anti-miasmatic theorists dating from Lucretius whose ideas had remained dormant in the medical literature up to the time of Fracastoro. The metaphor encouraged debate and dialogue and slowly began to direct scientific thinking away from a vaporous miasma and toward a tiny, even invisible, pathogenic organism external to the patient with the capacity for growth and reproduction. The full significance of the metaphor, of course, was dependent on the microscopic identification of these 'seeds of contagion' in the seventeenth and eighteenth centuries as described by Hook:

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[65] Lise Wilkinson, "The Development of the Virus Concept as Reflected in Corpora of Studies on Individual Pathogens," *Medical History* (January 1977) vol. 21, no. 1: 15-31, 18.

[66] Nutton, "Fracastoro's Theory of Contagion," *Osiris* vol. 6, 232.

> … the Earth itself, which lies so near us, under our feet shows quite a new thing to us, and in every little particle of its matter; we now behold almost as great a variety of Creatures, as we were able before to reckon up in the whole Universe itself.[67]

By the eighteenth and nineteenth centuries, these microscopic "Creatures" had become known as animalcules. However, the term virus lingered as well as a very non-specific term.

Athanasius Kircher (1602 CE – 1680 CE) was a seventeenth-century polymath whose reputation has fluctuated wildly among various scholars over time. Robert Koch's colleague, Friedrich Löffler, for example, gave a series of historical lectures in 1887 during which he was quite complimentary about Kircher's discoveries.[68] While Kircher did not cite the ideas of Fracastoro, he undoubtedly knew of his work and was influenced by his theory of animate contagion. Additionally the technology of the microscope was probably developed between 1620 and 1625 and appeared in Rome within a few years.[69] It had not been available to the more capable, but necessarily theoretical, Fracastoro. Kircher, however, even without any formal medical training, put the new instrument to immediate practical use during an epidemic that ravaged Naples and Rome in 1656. It was likely bubonic plague, and Kircher studied it carefully. This was still a very early period for microscopy, which had only been available for a few decades, but Kircher cleverly used a microscope to examine the blood of plague victims. He believed, as he wrote, that the blood was swarming with tiny "worms" that were invisible to the naked

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[67] Robert Hook, *Micrographia* (Istanbul: e-Kitap Projesi & Cheapest Books, 2014), 19. This is a reprint, and, for the most part, I have modernized spelling; I have also ignored italics and capitalization in these quotes.
[68] Lise Wilkinson, "Rinderpest and Mainstream Infectious Disease Concepts in the Eighteenth Century," M*edical History* vol. 28 (1984): 129-150, 129.
[69] Elizabeth F. Genung, "The Development of the Compound Microscope," *Bulletin of the History of Medicine* vol. 12 (1942): 576-579.

eye: "so crowded with worms as to well nigh dumbfound me … Plague is in general a living thing."[70]

Some historians of medicine are willing to credit his discoveries, while others insist on the impossibility of having seen truly microscopic pathogens with the primitive instruments of the time. In fact, it was pointed out as early as the nineteenth century that Kircher probably mistook inflammatory white blood cells and agglutinated red blood cells for what he believed to be microscopic pathogens.[71] Even so, Kircher's use of the new instrument seems to have been the first time it was employed to examine the bodily fluids of the sick. More importantly, though, Kircher's belief that he was seeing tiny, pathogenic organisms supports the contention that theories of contagion by means of such external, animate, and microscopic entities were current. Moreover, his announcement that he had visualized them would certainly have given added credence to such theories.

Additionally, historian Sally Smith Hughes asserts that Kircher was one of the earliest, post-classical scholars to identify the word, virus, with the concept of infection. Although he used virus for the venom of the tarantula, he also discussed the *virus pestiferum* and the *virus pestilens* in order to relate the concepts of virus and infection with the etiology of whatever epidemic illness struck the mid-seventeenth-century Italian cities.[72] Here we see, likely for the first time during Renaissance European history, the

[70] Quoted in John Glassie, *A Man of Misconceptions: The Life of an Eccentric in an Age of Change* (New York: Riverhead Books, 2012), 166.
[71] Fielding H. Garrison, *An Introduction to the History of Medicine*, 4th ed. (Philadelphia: W.B. Saunders, 1929), 253.
[72] Sally Smith Hughes, *The Virus: A History of the Concept* (New York: Science History Publications, 1977), 111.

dual use of the term virus to mean both a poisonous secretion and an external agent of infectious disease.

Early twentieth-century historian of medicine, Fielding Garrison, reckoned Kircher "was probably the first to employ the microscope in investigating the causes of disease … and he was undoubtedly the first to state in explicit terms the doctrine of a *contagium animatum* as the cause of infectious disease."[73] Moreover, the publication of his work preceded that of van Leeuwenhoek, and Kircher was widely read. Even if not always believed, his findings and theories kept alive and built upon Fracastoro's ideas as they circulated within the Italian *Respublica Literaria*. In retrospect, of course, it seems likely that having been impressed with Fracastoro's notion of seeds of disease, he was primed to actually see these seeds before he even put his eye to the lens of his microscope; nevertheless, keeping the idea of seeds of disease circulating within intellectual circles contributed to its currency. It does not matter, of course, whether he saw the pathogenic agent or not. He thought and argued that he saw microscopic organisms, and this added weight to the theory of external, infectious causation in the developing dialogue about the etiology of disease. Furthermore, of course, he considered them to be *living* organisms.

Perhaps the conceptualization of contagion during different time periods is best understood as a historical process changing over time, and especially crucial to the changes added by different thinkers were the technological innovations of their time periods. In this respect, even though Kircher was not the greatest of the thinkers, he benefited from his ability to apply the technology of microscopy to the problem,

[73] Garrison, *Introduction to the History of Medicine*, 252-3.

something his predecessor, Fracastoro, could not do. Later, in the early eighteenth century, Fracastoro's concept of seeds of disease would be invoked by Bernardino Ramazzini (1633 CE – 1714 CE) to explain the bovine disease, rinderpest, which had become epizootic around Venice in 1711. Ramazzini, professor of medicine at the University of Padua, disparaged any notion that the epizootic was the result of astronomical phenomena or the result of miasma, since it was quite specific to cattle. Fracastoro had also noted this specificity, but he did not develop its meaning as did Ramazzini.[74] The latter went on to state his idea in straightforward terms that serve perfectly well today: "It is an inherent characteristic of infections that the seeds of disease easily multiply and widely propagate themselves, if as they say, they find a lodging in a suitable and susceptible subject."[75] Ramazzini was a preternaturally acute observer of disease and humanity; it was he who first cataloged many occupational diseases; who first noted the strikingly low incidence of cervical cancer in nuns and other virgin females; and who first noted the importance of grave diggers in protecting the reputation of the medical profession, since "they bury not only the dead but the doctor's mistakes as well."[76]

The rinderpest epizootic among the Italian city-states led to a remarkable dialogue among several Italian scholars, including Carlo Francesco Cogrossi (1682 CE – 1769 CE) who carefully dissected the arguments for and against animate, rather than merely particulate, organisms as the cause of infectious diseases. In fact, Cogrossi was the first

[74] Fracastoro, *De Contagione*, 39.
[75] Quoted in, Wilkinson, "Mainstream Infectious Disease Concepts in the Eighteenth Century," 132.
[76] Franco Carnevale, "Ramazzini, Bernardino," in *Dictionary of Medical Biography*, eds. W.F. Bynum and Helen Bynum, vol. 4, (Westport: Greenwood Press, 2007), 1046-1049.

writer to convincingly specify that the contagious seeds were not inanimate material but rather were living organisms with the ability to replicate and multiply within host animals.[77] In fact, the utility of his theory quickly spread among his contemporaries with an Englishman extending his thinking to tuberculous consumption in 1720 and a Frenchman using the theory to explain the etiology of plague in 1721.[78]

The key to Cogrossi's 1713 revelation seems to have been the evidence presented by Giovanni Cosimo Bonomo (1663 CE – 1696 CE) in the late seventeenth century that human scabies was caused by mites. The mites had been seen, and remarked upon, by others for centuries, but Bonomo documented his remarkably complete microscopic findings in a letter of 1687.[79] In an English synopsis published in 1702, Bonomo described the causative agent, and at the same time, he explicitly rejected Galenic humoral theory. Opening a pustule on a diseased person, he found "a very small white *Globule*, scarcely discernable," and examining it with a microscope "found it to be a very minute Living Creature, in shape resembling a tortoise."[80] He described the ability of the mites to move from one host to infect another through skin contact. He went on to describe how these small creatures laid eggs and how they caused the signs and

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[77] Fracastoro had also written this, but not so persuasively; see Fracastoro, *De Contagione*, 57.

[78] Danièle Ghesquier, "A Gallic-Affair: The Case of the missing Itch-Mite in French Medicine in the early Nineteenth Century," *Medical History* (January 1999), vol. 43, no. 1: 26-54; 29.

[79] R.A. Roncalli, "The History of Scabies in Veterinary and Human Medicine from Biblical to Modern Times," *Veterinary Parasitology* vol. 25, no. 2 (July 1987): 193-198, 195-196. Danièle Ghesquier actually argues that Bonomo was not himself a confident microscopist and "entrusted the microscopic observations of his mites to the pharmacist [Diacinto] Cestoni who was an expert microscopist;" p. 37.

[80] Giovanni Cosimo Bonomo and Richard Mead, M.D., "An Abstract of Part of a Letter from Dr. Bonomo to Signor Redi, Containing Some Observations concerning the Worms of Humane Bodies," *Philosophical Transactions (1683-1775)* vol. 23 (1702-1703): 1296.

symptoms of scabies by "biting and eating, one single one happening sometimes to make several *Pustules*, of which I have often found two or three together."[81]

Bonomo specifically rejected "the Melancholy Humour of *Galen*" as a cause of this disease, the cause being "no other than the continual biting of these Animalcules in the Skin."[82] Thus, he was the first to clearly describe a specific, tiny pathogen causing a specific disease; the fact that it reproduced in the usual fashion by laying eggs rather than through spontaneous generation; and its means of burrowing in the skin which seemed to be the origin of the symptoms and signs. Furthermore, his repudiation of Galenic humoral theory shows that he was conscious of the importance of his theory in the construction of new knowledge.[83] He did not construct his theory on the old foundations of humoral theory; indeed, he recognized that he was replacing humoral theory with a totally new construction. Unsurprisingly, and largely because of the radical nature of his new theory, it did not succeed in convincing many. Skepticism was understandable as was reluctance to reject the humoral paradigm, which had adequately explained the etiology and physiology of human diseases for centuries. Most observers would have had little motivation to abandon an older paradigm to embrace a newer one, especially those not acquainted with microscopy.

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[81] Bonomo, "Observations concerning the Worms of Humane Bodies," 1297.
[82] Bonomo, "Observations concerning the Worms of Humane Bodies," 1297.
[83] Though many would prefer the use of the adjective 'social' before the word, construction, I agree with Worboys that omitting 'social' tends to emphasize the importance of biology and the importance of objective evidence in nature. While the construction of knowledge is a social process, it is usually subject to definite constraints imposed by nature and the evidence presented to the observer. See Michael Worboys, *Spreading Germs: Disease Theories and Medical Practice in Britain, 1865-1900* (Cambridge: Cambridge University Press, 2000), 12-13.

In this dialogue among Italian scholars one finds, in embryonic form, the basis of a conceptualization of microbial infections that resembles our present day understanding. In the philosophical schema of Thomas Kuhn, this was an early elaboration of the germ theory paradigm that would eventually, over time, gather new adherents who saw the world differently and who would find in the new paradigm more and better explanations of disease causation than could be found in the older humoral paradigm. Additionally, of course, the germ theory would explain many of the inexplicable anomalies that had arisen in the humoral paradigm. However, Kuhn also understood the importance of skepticism and reluctance to immediately embrace the new theory. Scientists are inherently conservative and try to preserve the accepted paradigm. And, this is good, because, as with political change (constitutional change, for example), it should be possible to undertake changes, revisions, or amendments; however, it should not be too easily accomplished. Otherwise political instability will be the norm, and that is seldom desirable. [84]

Alternatively, in the view of Eric Scerri, this dialogue among Italian scholars reflects the evolutionary growth of scientific knowledge. Each man was contributing to the overall growth of the scientific organism. Each observation, and its explanation was, the equivalent of a new branch of the evolving knowledge-based entity. In this case, the branches had the desirable traits needed to help them survive in the ever more empirical environment that was beginning to discount the importance of humoral explanations. Instead, the scientific setting was gradually developing the growing importance of an

[84] Thomas Kuhn, *The Structure of Scientific Revolutions*, 65 and 149-152.

ontological conceptualization of diseases and the usefulness of an understanding of animate contagion.

As with the complementarity of the sociological and scientific perspectives for examining the history of medicine, different, even competing, philosophies of historical knowledge should not be considered mutually exclusive. Scerri certainly contrasts his theories with those of Kuhn, but both have something to add to our understanding of the growth of medical and scientific knowledge. This is probably more evident when analyzing the work of different historical scientists and different historical episodes. Nevertheless, it can also be true (as in this case) when analyzing the work of a single historical actor and his theories. That is, the methods of both Kuhn and Scerri are useful, complementary, and add desirable nuance to the examination of historical episodes of scientific change.

The ability of the microscope to provide entry to an unknown realm of living things was crucial to the creation and acceptance of the new theory taking shape and became even more useful over time. In 1665, Robert Hook opined that, "by the help of microscopes, there is nothing so small, as to escape our inquiry; hence there is a new visible World discovered to the understanding."[85] Thomas Kuhn would say that when scientists changed from one paradigm to another they began to see the world differently.[86] Though this is not exactly what Kuhn had in mind, the microscope allowed scientists to, quite literally, see the world differently, seeing things previously unseen. In Eric Scerri's view the microscope was an evolutionary force within biology; it altered

[85] Hook, *Micrographia*, 19.
[86] Thomas Kuhn, *The Structure of Scientific Revolutions*, 111-113.

scientists' environment and allowed for a process of natural selection to act on competing theories.

It was this newly acquired, microscopic perspective that allowed them to begin making the transition to a new Kuhnian paradigm. Additionally, though, as noted earlier, it was also necessary to have an alternative, explanatory paradigm (at least one in the process of being developed) available before the older paradigm could be abandoned. This newer paradigm had been under construction for some time, at least since the time of Fracastoro. Mostly, however, it had been based on theory, and needed the empirical evidence of the microscope for additional support. On the other hand, the newly acquired ability to visualize aspects of a scientific puzzle does not guarantee that scientists will then determine the best explanation; they may still be confounded by Kyle Stanford's problem of unconceived alternatives, despite the newfound visual evidence.[87]

Cogrossi astutely put the work of Bonomo together with the findings of Kircher and the microscopic discoveries of Leeuwenhoek to create a new understanding of rinderpest based on,

> … tiny living creatures … so readily met with everywhere, and if they can penetrate into the most hidden recesses of animals, may it not be permissible to suspect that in the epidemic among oxen the poisonous insects can pass from one animal to another.[88]

Here was a well-studied, well-reasoned, and empirically based eighteenth-century antecedent of germ theory almost 150 years before the work of Pasteur and Koch. Moreover, it was being circulated within at least a portion of the Republic of Letters. It

[87] Stanford, *Exceeding Our Grasp*, 60-62, 128-131.
60-62.
[88] Quoted in Wilkinson, "Mainstream Infectious Disease Concepts in the Eighteenth Century," 135.

was not just 'something in the air;' rather, it consisted of ideas and theories based on empirical evidence and reasoned analogy. It was the result of rational human interaction with, and observation of, the natural world, and it was spread through the agency of natural philosophers whose scholarly discourse was instrumental to its dissemination.[89] By 1728, the English use of the term virus included "a poisonous substance in the body as a result of some disease, especially one capable of being introduced into other persons or animals by inoculation."[90]

Despite this progress in the understanding of disease specificity and external causation prior to 1820, the following decade saw a revival of belief in the internal, humoral, physico-chemical causation of diseases that denied both the external causation by animalcules and the specificity of diseases.[91] Thus, there was a period of controversy during which there was a vigorous dialogue among supporters of both theories. François-Joseph-Victor Broussais (1772 CE – 1838 CE) "believed that disease was provoked by cold air, drugs, miasmas or noxious substances in the atmosphere" and was thus was the champion of the more humoral minded physicians.[92] Countering Broussais and his allies were such leading lights as Pierre-Charles-Alexandre Louis (1787 CE – 1872 CE), René-Théophile-Hyacinthe Laennec (1781 CE – 1826 CE), and Pierre-Fidèle Bretonneau (1778 CE – 1821 CE). The latter wrote, "disease specificity is proven by so many facts that perhaps there is no truth which abounds more in demonstrations or is more fruitful;" he believed in a specific external etiological agent

[89] See for example, Worboys, *Spreading Germs: Disease Theories and Medical Practice in Britain, 1865-1900*, 12.
[90] Patrick Collard, *The Development of Microbiology* (Cambridge: Cambridge University Press, 1976), 159.
[91] Ghesquier, "A Gallic-Affair: The Case of the missing Itch-Mite," 38-40.
[92] Ghesquier, "A Gallic-Affair: The Case of the missing Itch-Mite," 39-40.

that combined with an internal susceptibility to produce a specific disease.[93] This, of course, is the 'crisis' stage to which Kuhn referred when an older paradigm begins to contend with a newer one, which has developed in response to anomalies encountered within the older paradigm.[94] The advocates of specificity and external agents of causation began to carry the day as more and more physicians were won over to the new paradigm of disease specificity.[95] Even so, what was most important was the highly sophisticated debate. It was part of a much larger, ongoing scientific dialogue that began to revolutionize early modern European thought into something more coherent and more congruent with the increasingly perceptible world of nature.

The microscope provided empirical access to what had been purely theoretical; there had been analogous reasoning from insects and ancient conceptions of 'seeds of disease,' but until the microscope, there had been no real evidence. With the aid of the microscope, aspects of the invisible became visually accessible, creating an entirely new world of observation and demanding new hypotheses to explain the revolutionary new microscopic observations. From these observations, which were essentially new data points, new hypotheses were developed that better fit the augmented data collection. Adding a new realm of observable and empirically verifiable microscopic entities significantly narrowed the number of competing hypotheses that could be used to explain the etiology of disease.[96]

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[93] Ghesquier, "A Gallic-Affair: The Case of the missing Itch-Mite," 40.
[94] Thomas Kuhn, *The Structure of Scientific Revolutions*, 66-91.
[95] Ghesquier, "A Gallic-Affair: The Case of the missing Itch-Mite," 40-41. See also, Kuhn, *The Structure of Scientific Revolutions*, 143-158.
[96] Stanford, *Exceeding Our Grasp*, 27-37. Stanford does not address this particular historical example; instead, his analysis examines this idea from the aspect of

Kircher actually examined a patient's blood and *believed* he saw microscopic organisms, and, while he probably did not, Van Leeuwenhoek certainly did. With the rapidly evolving technology of the microscope, the invisible organisms suddenly became apparent, making the theory of animate, microscopic *pathogens* real and no longer speculative. The new technology of microscopy, along with the observations of the scabies-causing mite, led to the realization that tiny, even invisible, creatures created at least some diseases, "finally and firmly [giving] reality to a vast world of hitherto invisible *animalcules*."[97] People began to question the relevance of the older, humoral paradigm, but before a transition to a new paradigm could occur, a new paradigm needed to be ready and waiting to replace the older one.[98] European science, however, did not yet have a completely fleshed out germ theory waiting to replace humoral theory. Even so, the dialogue continued and, Scerri might argue, sent out new branches by expanding to England.

On March 8, 1790, a Dr. George Wallis addressed the Medical Society in London and discussed the concept of virus as an etiologic agent and noted that the medical science of his day knew little "more of the particular nature of the virus creative of the Plague – Small Pox – Pemphigus – Cancer than the first observers [i.e. the ancients] of these diseases."[99] Lamenting the lack of empirical evidence for the nature of the viral

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contemporary philosophy of science and the way certain inferences tend to fit the data better and eliminate other, alternative inferences.

[97] Wilkinson, "Mainstream Infectious Disease Concepts in the Eighteenth Century," 131.

[98] Thomas Kuhn, *The Structure of Scientific Revolutions*, 77-79.

[99] George Wallis, "Annual Oration, *Delivered March 8th*, 1790, Before the Medical Society, Bolt Court, Fleet Street, London," (London: G.G.J. and J. Robinson, M.DCC.XC), 32-33. http://find.galegroup.com.proxy1.library.jhu.edu/ecco/retrieve.do?sgHitCountType=None&sort=Author&tabID=T001&prodId=ECCO&resultListType=RESULT_LIST&searchId

agent, "which might be examined, if any could, from the copiousness of the matter produced," Wallis noted that contemporary medical science understood the diseases only from their effects on patients: "but we, like them [Hippocrates, *et al*.], form our judgment only from the effects"[100] That is, the symptoms and the course of diseases were far better understood than were their etiologies. Nevertheless, Wallis' comments certainly show that the humoral paradigm of internal humoral imbalance was gradually being challenged by a conceptualization of disease as an ontological entity secondary to external causation. Even so, the idea of a virus remained, and would remain for over a century, very poorly defined, making it difficult for theorists to conceive of a plausible alternative to miasmatic theories of disease; the empirical evidence remained scanty, making it difficult to conceive of reasonable alternatives.[101] This situation also supports Kuhn's analysis of scientific change, demonstrating how protracted the process of change can be. Indeed, Kuhn's use of the term 'revolution' has proved unfortunate, connoting as it does, rapid change. Change was certainly not rapid in the situation outlined here; nor was it the case in Kuhn's paradigmatic example of the Copernican Revolution. The evidence is often available, and even understood by some, long before a significant change occurs in the scientific community at large.

=R1&searchType=BasicSearchForm&currentPosition=1&qrySerId=Locale%28en%2C%2C%29%3AFQE%3D%28A0%2CNone%2C13%29George+Wallis%3AAnd%3ALQE%3D%28da%2CNone%2C4%291790%3AAnd%3ALQE%3D%28BA%2CNone%2C124%292NEF+Or+0LRH+Or+2NEK+Or+0LRL+Or+2NEI+Or+0LRI+Or+2NEJ+Or+0LRK+Or+2NEG+Or+0LRF+Or+2NEH+Or+0LRJ+Or+2NEM+Or+0LRN+Or+2NEL+Or+0LRM%24&retrieveFormat=MULTIPAGE_DOCUMENT&userGroupName=balt85423&inPS=true&contentSet=ECCOArticles&&docId=CW3308249320&retrieveFormat=MULTIPAGE_DOCUMENT&docLevel=FASCIMILE&workId=CW3308249320&relevancePageBatch=CW108249320&showLOI=&contentSet=&callistoContentSet=ECLL&docPage=article&hilite=y accessed November 20, 2016.

[100] Wallis, "Annual Oration Before the Medical Society," 33.

[101] Stanford, *Exceeding Our Grasp*, 27-50.

Beginning his work in 1808 and continuing through the first half of the nineteenth century, an intelligent and discerning Italian lawyer turned agricultural investigator, Agostino Bassi (1773 CE – 1856 CE), was the first European to experimentally confirm the nature of a specific contagious disease and demonstrate the responsible microscopic organism.[102] Moreover, his achievement did not go unrecognized. Appearing "before a commission of nine professors of the I.R. university of Pavia in 1834," Bassi received (as he himself stated in the preface to his work) an official certificate attesting to the significance of his work.[103] The disease was muscardine, and it kills the silkworms so important to the Italian silk industry.[104] The pathogenic organism is a fungus. The commission noted that Bassi had established four important points. First, the crusty residue of the disease on dead silkworms is contagious and infects healthy silkworms. Second, the infectivity of the residue "can be destroyed by various chemical agents, harmless to the insect [silkworm]" even after it has contacted a healthy silkworm, if done promptly.[105] Third, the disease is highly infectious, because even a single dead silkworm can spread the infection throughout a breeding farm. Fourth, Bassi discovered various "chemical agents which can decompose and destroy this disease-bearing substance [the

[102] While Giovanni Bonomo had correlated his magnified view of the scabies mite with the skin disease, he had not really visualized a true microscopic organism; the mite was barely visible to the naked eye and had been noted before the advent of microscopy.
[103] Agostino Bassi, "Del Mal del Segno," trans. P.J. Yarrow, ed. with intro. By G.C. Ainsworth and P.J. Yarrow, in *Phytopathological Classics*, Number 10 (Baltimore: American Phytopathological Society, 1958), 1-2. Though he published his work in 1835, he finished well before then; he kept the work secret hoping to sell the information to alleviate his financial straits. He finally published when he realized no one was interested in buying the knowledge he had created dealing with control of the disease.
[104] It was also known as *calcinaccio, cannellino, calcino or calcinetto.*
[105] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 2.

crusty residue of the disease on dead silkworms] … to control the spread of the disease."[106]

Bassi was well aware of the importance of his findings, resolving as it does, "some of the many anomalies which the doctrine of contagious diseases in general contains."[107] He pointed out the necessity of acquiring as much empirical evidence as possible in order to understand why some of it will inevitably depart from the best explanation of the data: "It is always necessary to base one's calculations on the large number of similar facts, until time makes known to us the reasons which have caused a few of them to depart from the established principle."[108] In a remarkable paragraph, one can almost hear Bassi whispering to Thomas Kuhn down a dozen decades:

> Having learnt the present theory of calcification, the reader will be in a position to repeat the experiments on which I have based it, to carry out fresh ones, and perhaps even to find more effective or more rapid or more economical means of banishing the muscardine scourge than those which I propose.[109]

Bassi is telling his reader to learn what has been achieved by repeating the important experiments and then to begin the endeavor (which Kuhn would call normal science) of solving puzzles and advancing the field of knowledge within the paradigm that he, Bassi, has created.[110]

Bassi showed the disease never arises spontaneously, and that the "contagion is communicated by food, by inoculation, and by the mere contact of [infected] insects … [or] of any infected object, and even of air contaminated by the disease-bearing

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[106] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 2.
[107] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 3.
[108] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 3.
[109] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 3.
[110] See Kuhn, *Structure of Scientific Revolutions*, 1-9.

germs."[111] He clearly outlined the spread of contamination by virtue of air and wind disseminating the fungus; he discussed the role of animal vectors focusing on flies, which he noted, "can carry many kinds of contagion, if not all."[112] And, contrary to the reasoning inherent in humoral theory, he gave good, reasoned arguments why the infectious quality, "contagious virtue" of the disease must reside solely in the fungus and not in the host or the bad fumes and odors of the breeding establishments.[113] Amazingly, he described disease transmission by human hands carrying the seeds of the infecting fungus. This, of course, was the experimental information Ignaz Semmelweis would need two decades later to substantiate his own claims. Another observation germane to the work of Semmelweis discussed the fact that "amongst several adjoining breeding rooms, in all of which the fierce muscardine is present and in which conditions seem to be absolutely alike, the disease rages much more in one than in another."[114] Bassi attributed this to the "greater number of muscardine germs brought into or developed in a breeding room and spread around."[115] Semmelweis could have simply omitted the word 'muscardine' and changed 'breeding' to 'birthing' room in order to use Bassi's work in support of his own theory about puerperal sepsis.

Bassi described the life cycle of the fungus, including when it became infectious and how its spores spread, and he noted that its infectivity is not lessened over time "as it

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[111] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 8. Later in his monograph (page 39), Bassi despairs of convincing most breeders that the disease does not arise spontaneously.
[112] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, note #1, page 25.
[113] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 39-44.
[114] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, note #3, page 28.
[115] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, note #3, page 28.

reproduces itself over and over again, even in insects of a different species."[116] Even so, the pathogenic fungus only seems to live for about two years allowing an epizootic to die off. In extensive footnotes (some of which extend over more than two pages), Bassi detailed the macroscopic and microscopic appearance of the fungus and outlined the best methods of preparing the organism for microscopy. He also distinguished between pathogenic and non-pathogenic fungi with similar appearances, and by inoculating healthy worms with both varieties and showing only the pathogenic species caused disease, Bassi clearly anticipated Koch's postulates by several decades.[117] Bassi also described the appearance of the infection among a virgin population: "in a district where it has never raged … [it] quickly becomes epidemic, rages fiercely … [until it has] consumed them all except those that are immune by nature."[118] He then extrapolated these observations to "the contagions that afflict *man* and other animals," though he did seem to underestimate the numbers of infectious agents causing disease among humans.[119]

After 1844, Bassi began to broaden the scope of the theory he was developing from his empirical findings, fulfilling his motto: "When fact speaks judgment is silent, because judgment is the daughter of fact, not fact the son of judgment."[120] He analogically began to attribute diseases of humans, such as cholera, smallpox, plague, and

[116] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 9.
[117] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, notes 6-15 on pages 16-23. See also J.R. Porter, "Agostino Bassi Bicentennial (1773-1973)," *Bacteriological Reviews* (1973) vol. 37, no. 3: 284-288, 285.
[118] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 32.
[119] Bassi, "Del Mal del Segno," in *Phytopathological Classics*, 32 (italics added for emphasis).
[120] Ralph H. Major, "Agostino Bassi and the Parasitic Theory of Disease," *Bulletin of the History of Medicine* 26, no. 2 (July 1944): 97-107, 105.

rabies to microorganisms. He described the cholera bacillus decades before Koch and recommended boiling the utensils, clothing, and bed sheets of cholera patients. He preached the necessity of sterilizing needles used for vaccinations; and he discussed disinfection with chlorine and alcohol when Joseph Lister was still in medical school. He also developed a regimen for sterilizing the eggs of silkworms as well as the nurseries in which they were hatched.[121] He was limited, of course, by the rudimentary state of microscopy, his own failing vision, and the lack of adequate knowledge of staining techniques, which would be developed by Koch later in the century. Nevertheless, his work was exemplary, and he was indefatigable, still publishing his researches until his eightieth year.

Observations such as these would eventually lead to an intellectual atmosphere in which the work of Koch and Pasteur could build on the Romantic penchant for analogy and make the conceptual leap from fermentation to human disease. Technology, in the form of the microscope, came together with a new way of seeing the world less analytically and more metaphorically to produce the germ theory and finally displace the humoral theory. At the beginning of the nineteenth century, though, references to cowpox virus and smallpox virus did not indicate any specific or known disease causing entity. In an 1850 article, for example, the *Lancet* argued that it was through absorption into the victim's blood that "the virus of scarlatina, of hydrophobia, of typhus, of syphilis, &c." cause disease. Thus, virus, remained a generic term unqualified by, and unidentified with,

[121] Porter, "Agostino Bassi Bicentennial," 286-287.

any attributes of a specific disease.[122] Even in the late nineteenth-century, scientists used virus to simply mean "an agent of infectious disease [as in] Pasteur's dictum, 'Every virus is a microbe.'"[123] Likewise, after identifying and culturing the tubercle bacillus and then inoculating healthy animals with these bacilli to produce tuberculosis in 1882, Robert Koch wrote, "These bacilli are the real tuberculosis virus."[124]

Clearly, the creation of knowledge concerning bacteria and bacterial diseases progressed rapidly during the last four decades of the nineteenth century, and by the beginning of the last decade, scientists could reliably visualize and characterize bacteria with the light microscope. They could culture bacteria on artificial media and identify the colonies of specific bacteria. With the creation of the various graduated filters, it became possible to remove bacteria from solutions if, for example, it was desirable to separate them from any toxins they might produce. Thus bacteria were defined by their microscopic image; by the appearance of colonies on specific media; and by their size using filters with calibrated pore sizes.

On February 20, 1891, Edward Emanuel Klein delivered an enlightening lecture to the Royal Institution. Printed in two parts, it appeared in succeeding issues of *Nature* and nicely outlined the state of bacteriological knowledge and the investigative bacteriological methods available at the beginning of the last decade of the nineteenth

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[122] Quoted in Oxford English Dictionary, online edition (*Lancet* 15 June 1850: 711/1) http://www.oed.com/view/Entry/223861?redirectedFrom=virus#eid accessed October 31, 2016.
[123] Quoted in OED, online http://www.oed.com/view/Entry/223861?redirectedFrom=virus#eid accessed October 31, 2016.
[124] Requoted in K. Codell Carter, "Koch's Postulates in Relation to the Work of Jacob Henle and Edwin Klebs," *Medical History* (October 1985), vol. 29, no. 4: 353-374; 360.

century.[125] Klein pointed to the realization that various diseases "not previously suspected as communicable have a similar cause … and are therefore now classed amongst them."[126] That is to say, the finding and classification of communicable diseases was an ongoing process; not only were new ones still being identified, but "Not all infectious diseases which have been studied are due to Bacteria."[127] Late nineteenth-century microbiology was consciously aware of the existence and continued discovery of new pathogenic organisms outside the world of bacteria. Furthermore, it is not anachronistic to use the term 'microbiology' in describing scientific knowledge at this time, because the first course in microbiology was taught at the Sorbonne in 1879. It was soon followed by Koch's own course in 1884 at the University of Berlin and another in London in 1886.[128] Widespread knowledge and acceptance of the new germ theory thus began sometime between 1876 and 1884.

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[125] E. Klein, "Infectious Diseases, Their Nature, Cause, and Mode of Spread I," *Nature* (March 5, 1891), vol. 43, no. 1114: 416-419 and "Infectious Diseases, Their Nature, Cause, and Mode of Spread II," *Nature* (March 12, 1891), vol. 43, no. 1115: 443-446. Though born and educated in Vienna, Klein emigrated to Britain in 1871; he was crucial to keeping British science apprised of continental advances and to establishing and maintaining British bacteriology into the first decades of the twentieth century; see his obituary, "E.E. Klein, M.D., F.R.S.," *British Medical Journal* (February 21, 1925), vol. I: 388.

[126] Klein, "Infectious Diseases, Their Nature, Cause, and Mode of Spread I," 417. Norman Howard-Jones opined that the first use of the term, 'communicable,' was in a pamphlet by Sir Gilbert Blane commenting on the approach of cholera; see Howard-Jones, "Fracastoro and Henle: A Re-Appraisal," note #24, page 66. However, Robert Patterson, in an 1841 publication, quoted another physician, who said, "A patient was sent to me affected with a singular species of molluscum, which appears to be communicable by contact;" in Robert Patterson, "Cases and Observations on the Molluscum Contagiosum of Bateman, with an Account of the minute Structure of the Tumours," *Edinburgh Medical and Surgical Journal* (1841), vol. 56: 279.

[127] Klein, "Infectious Diseases, Their Nature, Cause, and Mode of Spread I," 418.

[128] Hughes, *The Virus: A History of the Concept*, 27.

Conveniently for historians of science, Klein used the term 'virus' in his article, illuminating for historians at least one of its contemporary meanings for nineteenth-century scientists and microbiologists. Klein was discussing the spread of certain diseases and their portals of entry into the human body, included among these diseases were cholera, rabies, tetanus, smallpox, and tuberculosis. He said, however, "this does not mean that the virus is necessarily limited to one particular portal."[129] Even though Klein was using the word virus in a generic sense and referring to different diseases, he was nonetheless referring to a particulate and an animate entity able to enter the human body, cause disease, replicate, and travel from one host to another. So, in 1891, a virus was reimagined as an unspecified type of microbe, and *The New Sydenham Society's Lexicon* defined it as "A poison or micro-organism which causes a morbid process or disease."[130]

The term 'microbe' suggests a microscopic organism: something visualized microscopically. Scientists began capturing bacterial pathogens from infected tissues by trapping them with filters designed to restrict the passage of certain size particles. The material could then be grown on newly designed culture media for macroscopic identification based on the appearance of different colonies. The individual bacteria were then isolated and stained in order to reveal their microscopic structure and appearance. However, such techniques were not always successful. There were some diseases of both plants and animals that did not seem to cooperate with the new techniques. For example, the *in vitro* culture of bacteria required the correct nutrient media, which was not always easy to determine. Naturally, when such efforts failed, the failure was much more likely

[129] Klein, "Infectious Diseases, Their Nature, Cause, and Mode of Spread I," 418.
[130] Power and Sedgwick, *The New Sydenham Society's Lexicon of Medicine and the Allied Sciences*, Vol. V.

to be ascribed to incorrect media than to the existence of a totally unknown organism of undetermined character.[131] Importantly, it was also acknowledged by about 1875 that light microscopes could not be improved indefinitely to reveal ever-smaller objects. Scientists knew the resolving power of light microscopy was limited by the wavelength of light, meaning that objects smaller than the wavelength of light could not be visualized. By about 1890, that limit had been reached.[132] Light microscopy was not going to allow scientists to see viruses as distinctive animate particles the way bacteria could be seen and characterized. Instead, remaining invisible, viruses would have to be conceptualized differently and this was the work of early microbiologists, establishing a new discipline of virology.

[131] Hughes, *The Virus: A History of the Concept*, 35.
[132] Hughes, *The Virus: A History of the Concept*, 32-33.

Chapter 2

The Beginnings of Virology, 1886-1904

In the late 19th century, a disease that mottled and damaged the leaves of their tobacco plants, the important, saleable part of the crop, troubled Dutch farmers. The lack of any organized, or centralized, knowledge about the pathological condition was reflected in the numerous local names for the same disease. It was variously called bunt, smut, or rust based on the visual appearance of the affected vegetation, and these terms were used generically to describe other, usually fungal, diseases of wheat or other crops. However, because this purely descriptive conceptualization offered no understanding of the etiology of the disease or how to control it, the developing science of plant chemistry was enlisted to help. As Adolph Mayer would write in his 1886 landmark paper, "it [seemed] to be very important to draw the attention of the agricultural sciences; because the harm done by this disease is often very great … it has caused the cultivation of tobacco to be given up entirely" in certain places.[133]

The young, thirty-six-year-old Mayer had trained as a chemist, following in the footsteps of his maternal grandfather and great-grandfather, both of whom were renowned German chemists, Leopold and Johann Friedrich Gmelin. He began his investigations of the disease in 1879 and published his findings in Dutch in 1885 and

[133] Adolf Mayer, "Concerning the Mosaic Disease of Tobacco," (1886) in *Phytopathological Classics: number 7,* translated by James Johnson (Ithaca: Cayuga Press, 1942), 11.

German in 1886, a time period during which Louis Pasteur was also diligently working to conceptualize rabies, another poorly understood transmissible disease. Knowledge of infectious and contagious diseases caused by the newly minted term, microbes, was increasing rapidly. For the most part, however, only bacteria, funguses, and parasites such as nematodes were visible and empirically accessible. The invisible viruses could only be understood theoretically.

Mayer, in fact, began by defining the disease in terms of its visible symptomatology,

> … a map or mosaic-like coloring of light and dark green appears on the leaf surfaces … Soon afterwards one can … discern that the leaf shows a more pronounced growth in thickness in the darker colored spots … Finally, some of the lighter and thinner parts of the leaf die prematurely … when a leaf has become diseased, all the younger leaves of the same plant also show the symptoms in corresponding earlier states.[134]

All of these changes destroy the quality of the tobacco leaves making them unfit for cigar production, and Mayer noted somewhat tartly that the disease is also "harmful to the aroma, so far as one can speak of such in European tobacco."[135] Mayer began by defining the disease according to its empirically visible aspects, suggesting "as an international name 'mosaic disease of tobacco'" (TMD) because of the discoloration of the leaves. He also tried to dispel the notion that there was more than one form of the disease.[136] This empirical description, however, was inadequate as would be pointed out a few years later by Dmitrii Ivanowsky who showed that Mayer's description, and photographic illustration, really reflected the existence of two diseases simultaneously affecting these

[134] Mayer, "Concerning the Mosaic Disease of Tobacco," 11-12.
[135] Mayer, "Concerning the Mosaic Disease of Tobacco," 12.
[136] Mayer, "Concerning the Mosaic Disease of Tobacco," 13.

Dutch tobacco plants. Ivanowsky argued that the other disease, known as the pock-disease, was not infectious.[137]

In an article examining the origins of modern virology, Marian Horzinek argued that during Mayer's work, "no attempts were made to elucidate the character of the infectious principle."[138] This assertion, however, is debatable, because Mayer exhaustively summarized the theories and the state of knowledge with which he was confronted at the beginning of his investigations and carefully examined all aspects of a possible infectious etiology. Moreover, he specifically noted the importance of mentioning "experiments that led only to negative results" in an effort to eliminate certain ways in which the disease could be defined.[139] TMD had been variously attributed to poor fertilization, the weather, too much sun, frost, fogs, poor seed quality, imperfect soil, or faulty technique in planting, and Mayer considered them all thoroughly before rejecting them and starting over at the very beginning. Altogether, he devoted several years of research to ruling out various theories of causation, even allowing growers to direct his experiments to evaluate their own favorite beliefs about the etiology such as specific types of damage to young seedlings during the process of planting.

Following this, and making the most of his training as a chemist, he undertook chemical examinations of the normal and diseased plant tissues to rule out possible nutritional factors associated with soils or fertilizers that might be at fault. Describing this

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[137] Dimitrii Ivanowsky, "Concerning the Mosaic Disease of the Tobacco Plant," (1892) in *Phytopathological Classics: number 7,* translated by James Johnson (Ithaca: Cayuga Press, 1942), 27.
[138] Marian C. Horzinek, "The Birth of Virology," *Antonie van Leeuwenhoek*, vol. 71, issue 1-2 (February 1997): 15-20, 17.
[139] Mayer, "Concerning the Mosaic Disease of Tobacco," 14.

as “the scientific treatment of technical agricultural questions,” Mayer left no doubt that he was aware that his investigations reflected the application of the new technology of chemical engineering to a practical problem of plant pathology, and he was able to eliminate the possibility of a nutritional cause.[140] Visible pathogens such as fungi and nematodes were also carefully and thoroughly eliminated through diligent inspection of soils, seedlings, roots, and plants.

Horzinek noted correctly that late nineteenth-century scientists researching TMD were somewhat oblivious to the possibility that the agent they were dealing with was fundamentally different from the bacteria.[141] This is an important point, because it echoes the ideas of many philosophers of science, including Ludwig Fleck, Norwood Russell Hanson, as well as Kuhn, who all pointed to the theory-laden observations of most scientists. That is, almost all of these scientists approached the understanding of viruses with minds influenced by what they already knew. What they knew, of course, was not incorrect; it was simply not applicable to the new situation. The ingenious Louis Pasteur did somewhat better, speculating in 1884 that the cause of rabies was a “micro-organism infinitesimally small.”[142] Even so, even he was not able to go much beyond that appraisal. Because nothing could be seen or cultured, his reasoning was not based on empirical evidence. It was more likely based on his intuitive use of analogy: if, for example, bacteria had previously been invisible, then other types of pathogens could remain so.

[140] Mayer, “Concerning the Mosaic Disease of Tobacco,” 11.
[141] Horzinek, “The Birth of Virology,” 17.
[142] Horzinek, “The Birth of Virology,” 17.

Importantly for Adolph Mayer in Holland, the year 1881 allowed for the cultivation of foreign varieties of tobacco on previously uncultivated land, and Mayer soon noticed "it was striking that all the foreign varieties of tobacco … were entirely spared by the disease, while in the rest it never was entirely absent."[143] The crucial element seemed to be something in the soil resulting from the prior presence of diseased plants. Over the next year, he developed this observation by varying aspects of tobacco cultivation in order to test other possibilities and found all other circumstances were insignificant. The only important variable associated with the disease was whether or not the soil had harbored diseased plants in the past. Because the evidence suggested the disease was transmitted to the plants from the soil, he began infer an infectious etiology: "the conjecture that we were dealing with a disease caused by parasites was naturally strengthened."[144] This, of course, had been a likely possibility from the beginning but had been rejected when careful investigations failed to reveal any fungi, microscopic organisms, nematodes, or other visible pathogens. Unfortunately, this is where Mayer's very careful and detailed narrative of his methods and experiments disappoints the reader interested in his thinking and analysis.

Mayer wrote, "Then, I suddenly made the discovery that the juice from diseased plants obtained by grinding was a certain infectious substance for healthy plants."[145] He carefully describes how he ground a diseased leaf with a small amount of water to create an emulsion for injection into a healthy leaf, but he gave no explanation of his epiphany or why he thought of this experiment. All of his other procedures and the reasoning

[143] Mayer, "Concerning the Mosaic Disease of Tobacco," 19.
[144] Mayer, "Concerning the Mosaic Disease of Tobacco," 19.
[145] Mayer, "Concerning the Mosaic Disease of Tobacco," 20.

behind them were carefully detailed, but not this crucial step. He had earlier included a footnote along with a very brief and unenlightening reference to work done in 1881 looking for soil-based parasites in which, he wrote, "my attention had been drawn by the studies on flax blight that I was making at the same time."[146] So, perhaps he was reasoning analogously from this earlier investigation.

In any event, probably based on his prior observations of diseased plants associated with apparently diseased soil, he hit upon the idea of directly transferring tissue from one plant to another and was immediately successful. Thus, he was able to add to the definition of TMD, expanding the conceptualization of the disease, and its agent, beyond the obvious, visible effects. It became a transmissible disease and quite contagious as healthy seedlings planted in diseased soil routinely acquired the disease. Moreover, he was able to stipulate several other defining qualities. First, the incubation period of the agent was 10 or 11 days. Second, its virulence was dependent on the age of the inoculated plant rather than on the amount of the inoculum. And third, its appearance was "not in the leaf that has been inoculated, but in the very youngest leaves, particularly those not yet developed at the time of inoculation."[147] Though, he does not seem to have realized it, this last finding, that the disease affected primarily younger leaves rather than the one receiving the inoculum, meant that the causative agent was distributed systemically through the plant. Though Mayer missed the significance of this, a later investigator, Martinus Beijerinck, did not. As we shall see below, Beijerinck concluded from this finding that the agent reproduced in the cells of growing tissues and not in older, no longer dividing, cells.

[146] Mayer, "Concerning the Mosaic Disease of Tobacco," 16-17.
[147] Mayer, "Concerning the Mosaic Disease of Tobacco," 20.

Mayer's successful transmission of TMD, of course, prompted more intense microscopic examination of tissue fluids as well as isolation of various particulate matter in order to search for bacteria and to test for infectivity. This involved tests with more than a dozen other possible candidates including several known bacteria, various manures, other plant materials, and even moldy, old cheese. Having failed to define the disease further through empirical observation, Mayer filtered the fluid inoculum, which he knew to contain the contents of cells as well as whole cells. As long as the filtrate contained particulate matter, it was infectious, but after repeated filtrations that removed all particles, Mayer seems to have determined that the solution had lost its infectivity.[148] This led him to conclude, incorrectly as it turned out, that he was dealing with a bacterial infection.[149]

In Russia, a meticulous, young botanist, Dmitrii Ivanowsky, had begun studying the tobacco mosaic disease about the time Mayer was publishing his own findings.[150] Ivanowsky's findings would begin an important debate within germ theory that would ultimately generate the field of virology. First, as noted above, Ivanowsky believed Mayer had actually conflated two diseases into one.[151] This, of course, was incidental to Mayer's work in demonstrating the infectious nature of TMD, which Ivanowsky readily

[148] This was an inexplicable error on Mayer's part and clearly at odds with the results of later investigators.
[149] Mayer, "Concerning the Mosaic Disease of Tobacco," 22-24.
[150] Hubert Lechevalier, "Dimitri Iosifovich Ivanovski," *Bacteriological Reviews* (June 1972), vol. 36, no. 2: 135-145, 137.
[151] James Johnson who translated and introduced the classic papers of Mayer, Ivanowsky, and Beijerinck in 1942 noted that Mayer was likely correct that they were dealing with a single disease and Ivanowsky was incorrect in believing them to be two separate diseases. See, James Johnson, "Translator's Preface," in *Phytopathological Classics: number 7,* translated by James Johnson (Ithaca: Cayuga Press, 1942), 6.

acknowledged; nevertheless, it was for Ivanowsky the crucial finding and purpose of his paper:

> the remarks under consideration have only the purpose to establish the independence of the two diseases, the mosaic and the pock disease, and to prove that they do not represent as Ad. Mayer assumes, different stages of development of one disease.[152]

Of much greater significance to the history of virology, though, was Ivanowsky's assertion that Mayer's belief that infectivity could be removed from his solutions by filtration through filter paper, even numerous such filtrations, was incorrect. It was only within the penultimate paragraph of his paper that Ivanowsky contradicted "most emphatically [Mayer's] statement that the sap of leaves attacked by mosaic disease loses all its infectious qualities after filtration through double filter paper."[153]

The significance of Ivanowsky's paper is twofold. On the one hand, he filtered the infectious solution with a new Chamberland filter that he was confident could, and did, remove bacteria and found it was still infectious.[154] Thus, he amended Mayer's erroneous interpretation: the filtered fluid remained infectious after removal of bacteria. On the other hand, because the fluid remained infectious, Ivanowsky's work began a scientific dialogue among early researchers that would begin to define the characteristics of viruses and create a new classification of pathogenic agents. This dialogue was of great importance, since it would considerably widen the scope of the germ theory itself. Ultimately, it would lead to an ongoing understanding of viruses and viral diseases, establishing the field of virology.

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[152] Ivanowsky, "Concerning the Mosaic Disease of the Tobacco Plant," 30.
[153] Ivanowsky, "Concerning the Mosaic Disease of the Tobacco Plant," 29.
[154] Ivanowsky, "Concerning the Mosaic Disease of the Tobacco Plant," 30.

However, modern commentators are often too quick to credit Ivanowsky with establishing the concept of the virus and the field of virology.[155] It is often argued, in somewhat whiggish fashion, that Ivanowsky began the triumphal march of scientific knowledge about viruses that has culminated in our present-day understanding of viruses and viral diseases: "this filtration experiment … was the first step in the discovery of viruses."[156] In fact, however, he could not really have imagined a virus as we know it today, and one biographer even argues that Ivanowsky studiously avoided "imaginary explanations [because they] tend to conceal existing gaps in knowledge and are thereby detrimental to science."[157] Moreover, his inability to conceptualize a totally new sort of pathogen, rather than think of it as a very small conventional microbe, was shared by other great nineteenth-century scientists, such as Pasteur, Löffler and Frosch. As Wilkinson says, "Having fought hard to establish the principle of a living, cellular microbe as a specific agent for every infectious disease, neither Pasteur nor Koch was yet ready to consider other possibilities."[158] What Ivanowsky actually did was to start the dialogue and begin the process of conceptualization that would gradually define viruses, a process that would continue through the first half of the twentieth century.

Employing the new Chamberland filters, introduced by Charles Chamberland in 1884, Ivanowsky was able to add critical new information to the conceptualization of the pathogenic agent: it was filterable. That is, it passed through ultrafine filters that normally

[155] Alice Lustig and Arnold Levine, "One Hundred Years of Virology," *Journal of Virology* vol. 66, no. 8 (August 1992): 4629-4631, 4629; and W. M. Stanley, "Soviet Studies on Viruses," *Science* (February 1944), vol. 99, no. 2564: 136-138.
[156] Lustig and Levine, "One Hundred Years of Virology," 4630.
[157] Lechevalier, "Ivanovski," *Bacteriological Reviews*, 138.
[158] Wilkinson, "The Development of the Virus Concept," 24.

trapped, and removed, bacteria.[159] Modern scholars have correctly argued that the ability to pass through bacterial filters constituted "an experimental definition."[160] As already discussed, Mayer thought he had removed the infectious quality of the sap by filtration through doubled filter papers. While Ivanowsky corrected this error and showed the filtered sap remained infectious, he still believed he was dealing with a bacterial disease. Any other hypothesis would have involved the kind of "imaginary explanation" that he avoided "as detrimental to science." In reality, an extremely small bacterium was more likely than a totally new and previously unknown organism. Thus, Ivanowsky, like Mayer and Beijerinck, using techniques of bacterial research, favored the possibility of an unusually small bacterium or a bacterial toxin as the causative agent. The toxin of diphtheria infection had only been discovered a few years earlier and its known passage through Chamberland filters presented Ivanowsky with a ready (bacterial) explanation for the infectious quality of the filtered fluid.[161] Decades later, virologists were still using the term 'filterable virus' in a very general fashion denoting "certain active transmissible agents which are capable of producing pathological conditions" even when they believed that many were likely caused by conventional bacteria of extremely small size that, like viruses, were filterable.[162]

Nevertheless, scientists building on Ivanowsky's work would be better positioned to study the agent now that it could be isolated from other known agents such as bacteria.

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[159] Working in Pasteur's laboratory, Chamberland designed porcelain filters of varying pore sizes to selectively separate bacteria of different sizes. See Stuart Mudd, "Filters and Filtration," in *Filterable Viruses*, ed. Thomas Rivers (Baltimore: Williams & Wilkins, 1928), 55-94.
[160] Lustig and Levine, "One Hundred Years of Virology," 4629.
[161] Lechevalier, "Ivanovski," *Bacteriological Reviews*, 140.
[162] Thomas Rivers, "Some General Aspects of Filterable Viruses," in *Filterable Viruses*, ed. Thomas Rivers (Baltimore: Williams & Wilkins, 1928), 55-94.

Horzinek is correct that, like new technologies in general, this innovation marked a major turning point in viral research.[163] On the other hand, though, Ivanowsky was less certain of his discovery than many commentators would have it in their desire to establish a father of virology. While, Ivanowsky did first filter a virus, he nevertheless believed that the infectivity of his filtrate could "be explained most simply by the assumption of a toxin secreted by the bacteria present, which is dissolved in the filtered sap."[164]

When Adolf Mayer arrived at Wageningen, Holland in 1879 to begin his study of the mosaic disease of tobacco, Martinus Willem Beijerinck was already there, studying bacteriology and the microbiology of soils. The two men knew each other and sometimes worked together. While Beijerinck is often thought of as a botanist, he actually trained as a chemist and his closest friend, sometime roommate, and mentor, J.H. Van't Hoff won the first Nobel Prize given in chemistry; even so, botany was Beijerinck's first love. Recall that Mayer had been unable to isolate or identify any bacterial agents in his own search for what he believed to be a bacterial agent in tobacco mosaic disease. Accordingly, Mayer encouraged his younger associate to improve his own knowledge of bacteriological research and techniques. Beijerinck did so, studying with a German physician, turned botanist and plant pathologist, Anton de Bary, who was instrumental in determining that the Irish potato blight was a fungal disease, an important milestone in understanding the pathophysiology of plants.[165]

Beijerinck's work with de Bary and with Emil Hansen, another noted bacteriologist, furthered his own bacteriological skills to the point that he was able to

[163] Horzinek, "The Birth of Virology," 17.
[164] Ivanowsky, "Concerning the Mosaic Disease of the Tobacco Plant," 30.
[165] Lechevalier, "Ivanovski," *Bacteriological Reviews*, 136.

successfully isolate bacteria from plant root nodules.[166] However, at this time, the idea of plant pathogens had not extended beyond fungi to bacteria, and the concept of the virus remained quite nonspecific. More importantly, although the techniques he learned were the most advanced and sophisticated of the day, they were developed in conjunction with work to elucidate the nature and structure of a known type of organism: bacteria. Bacteriological techniques would primarily help show that a bacterium was *not* the pathogenic organism and help show what qualities the actual agent did *not* possess. Nevertheless, Beijerinck, who was a workaholic and devoted to scientific research, became a very successful microbiologist. Rather sadly, though, he was a testy and lonely recluse who spurned the company of others and lived his life in seclusion with his two unmarried sisters.[167]

In his 1898 paper, "Concerning a Contagium Vivum Fluidum as a Cause of the Spot Disease of Tobacco Leaves," Beijerinck noted his professional association with Mayer, but also that he had not yet developed his skills in bacteriology and was little help to his older colleague. Nevertheless, he was well acquainted with Mayer's work, and over the course of the next decade began his own studies ruling out any bacterial component to the infection: "the conclusion was no longer to be denied, that the spot disease is an infectious one that is not caused by microbes."[168] Beijerinck had unwittingly repeated the filtration experiments of Ivanowsky, and "It soon became evident that the sap of diseased

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[166] Hughes, *The Virus: A History of the Concept*, 117 and 48.
[167] King-Thom Chung and Deam Hunter Ferris, "Martinus Willem Beijerinck (1851-1931)," *American Society for Microbiology News*, vol. 62, no. 10 (1996): 540-541. See also, Waterson and Wilkinson, *History of Virology*, 27.
[168] M.W. Beijerinck, "Concerning a Contagium Vivum Fluidum as a Cause of the Spot Disease of Tobacco Leaves," (1898) in *Phytopathological Classics: number 7,* translated by James Johnson (Ithaca: Cayuga Press, 1942), 34.

plants remains infectious when filtered through porcelain."[169] He carefully checked the filtrate for any evidence of bacteria, and ruling this out, he declared the filtered sap to be sterile, even though it remained infectious.

This is an important point, because his use of the term 'sterile' is not congruent with its present use; that is, most would not consider the fluid 'sterile' if it transmitted disease. Beijerinck, of course, simply meant that it was devoid of those microorganisms already known, and no bacteria could be cultured from the fluid. Part of the difficulty was determining whether the pathogen was a living entity, such as a bacterium or fungus, or whether it was simply a chemical compound. The fact that it was not removed by filtration designed to remove known particulate and animate pathogens, especially cellular structures, suggested it was chemical, but its ability to replicate itself in plants argued for some life form, even though this seemed to contradict Virchow's belief that all life arose from cells.[170]

Without any knowledge of the work of either Ivanowsky or Beijerinck, Friedrich Löffler and Paul Frosch were simultaneously performing the same filtration experiments with an animal pathogen that caused bovine foot and mouth disease. They carried the filtration experiment further than Beijerinck by ruling out the presence of a toxin through quantitative analysis. Moreover, after passage through numerous animals, it did not lose its potency. They concluded it must be a living agent that could reproduce and thereby continually maintain or increase its pathogenicity. Much like Mayer and Ivanowsky they believed the agent to be a minute, microscopically invisible bacterium that was simply

[169] Beijerinck, "Concerning a Contagium Vivum Fluidum," 34.
[170] Hughes, *The Virus: A History of the Concept*, 48-52.

much smaller than those already known and described.[171] Kuhn described this situation where "Normal science … suppresses fundamental novelties" and newfound anomalies are not thought to question the paradigm (bacterial causation of infectious disease); instead, they are simply incorporated into the paradigm by making minor adjustments (bacteria of unusually small size that pass through Chamberland filters).[172] Furthermore, Mayer and Ivanowsky were not alone in their adherence to the idea of invisibly small bacteria.

The work of Löffler and Frosch, recall, had lent credence to the idea that these invisible microbes might simply be conventional organisms that were simply much smaller, and thus, invisible. Guiseppe Sanarelli summed it up nicely in 1898:

> … since it is unlikely that there are unorganized [noncellular] infectious agents in nature, one is indeed compelled to believe that certain diseases are produced by organisms which are so small that they are scarcely visible to the human eye, even when it is aided.[173]

Over and over in the course of this late nineteenth-century dialogue, one sees that microbiologists were reluctant to admit the existence of something of which they had difficulty conceiving, something outside the realm of knowledge already created within the paradigm of bacterial germ theory.

Moreover, Edmond Nocard and Emile Roux worked with the bacterial agent of bovine pleuropneumonia, and had to develop new techniques to prove the filterable agent was a bacterium at the very limits of light microscopic resolution. First, they had to culture the organism in order to isolate it and use it to infect healthy animals, but the

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[171] Hughes, *The Virus: A History of the Concept*, 62-63.
[172] Thomas Kuhn, *The Structure of Scientific Revolutions*, 5.
[173] Quoted in Hughes, *The Virus: A History of the Concept*, 67.

mycoplasma bacteria was, like the agent of tobacco mosaic disease, refractory to all methods of culture. Initially invisible and impossible to culture, it was very much like Beijerinck's *contagium fluidum*. Nevertheless, Nocard and Roux were able to develop a completely new method of culture involving the surgical implantation of sticky, collodion pouches, filled with organic, nutrient compounds, into rabbits. This was not exactly an *in vitro* process of culture. It was entirely unique and adapted to this specific organism; it was, in fact, an *ad hoc* undertaking. Even after growing thousands of mycoplasma, they were only barely able to visualize them with the light microscope.[174] Obviously then, microbiologists were making progress in identifying, at least some of, these filterable agents as vanishingly small bacteria, and this bestowed considerable plausibility on the suspicion that all were simply tiny bacterial elements.

Nevertheless, ruling out bacteria and those 'microbes,' which he, and late 19th-century science knew and understood, Beijerinck began using the term 'virus.' And, he seems to have been working towards using it in contradistinction to bacterium. Virus had been a usefully generic term for many centuries. Recall that it indicated something noxious, and was used for venoms, poisons, and even noisome vapors.[175] It had not been used to denote any specific, pathogenic agent, with known properties, the way that bacterium had been used in the nineteenth century with the advent of the germ theory. So, even though he used the term 'virus' in his paper to describe the agent of infection, he was not necessarily implying specific properties. Nor, was he suggesting an organism, such as scientists were able to visualize with electron microscopy five years after the invention of that device in 1934. In fact, Beijerinck also used the term 'contagium' to

[174] Hughes, *The Virus: A History of the Concept*, 64-67.
[175] Horzinek, "The Birth of Virology," 15.

refer to this essentially unknown agent of infection; nonetheless, he added crucial ideas to the definition and conceptualization of viruses as agents of disease somehow different from bacteria and other known microbes.

Because of his total immersion in the scientific knowledge of the day, Beijerinck completely missed the significance of the fact that, several generations earlier, there had been no microbes at all to even consider. It should not have been conceptually difficult to imagine a novel category of organisms too small to visualize with the microscope, since it had only been slightly more than a century since Van Leeuwenhoek had revealed the microscopic world to scientists. Both telescopes and microscopes were constantly being improved and increasingly revealed more previously unknown objects. Why should anyone think that the limits had been reached; why should one not expect more and more to be revealed? In fact, as already noted, Pasteur did speculate that the cause of rabies was an invisible organism much smaller than any known at that time. Likewise, at the same time Beijerinck was working with a plant pathogen, Friedrich Löffler performed the same experiments studying bovine foot and mouth disease, and he, unlike Beijerinck, did not consider just a toxin. Instead, Löffler *was* able to make the conceptual leap to include the possibility of an unknown pathogen that could replicate itself.[176] Instead, Beijerinck focused on whether the agent was particulate or simply a solution.

Beijerinck, like Ivanowsky, used a porcelain filter to remove particulate microbes, and, having done so, he considered the still infectious solution to be "entirely sterile."[177] However, he was using the term, contagium, and he needed to determine if it was a *contagium fixum* or a *contagium fluidum*; that is, was the agent particulate or completely

[176] Horzinek, "The Birth of Virology," 17-8.
[177] Beijerinck, "Concerning a Contagium Vivum Fluidum," 35.

soluble? He noted, for example, that "the corpuscular nature of the contagium has not been entirely disproved," and if it were corpuscular, it would be a *contagium fixum*.[178] He began using the word virus and needed to better define the term, so he designed an ingenious experiment to

> separate the virus from the raw leaf substance, as well as from all bacteria, through diffusion, since the virus, if at all capable of diffusion, could penetrate into the agar downwards and sideways … [to determine] whether the contagium was actually capable of diffusion and, accordingly, had to be considered as soluble in water, or if not capable of diffusion, therefore, as extremely minutely distributed, yet as corpuscular, that is, as *contagium fixum*. [179]

He could then test the agar itself for infectivity. Not only was agar, remote from the initial point of plating, infective but the infectivity decreased as the distance increased proving to his satisfaction "that the virus must really be regarded as liquid or soluble and not as corpuscular."[180] Thus, it was, for Beijerinck, a *contagium fluidum*. Because his repudiation of its corpuscular nature was based on the dimensions of particulate matter that could be filtered, visualized, or diffused though agar at the turn of the century, his use of 'virus' was not unlike that of the ancients who used it to refer to venom or to the poisonous saliva of rabid animals.

Ivanowsky read of Beijerinck's work and repeated the diffusion studies through agar. Interestingly, however, *he* began to conceptualize the infective agent as a particulate entity and used India ink (a suspension of tiny carbon particles) as a model for a particulate agent suspended in the infectious sap. He found that India ink particles also diffused through older agar, though not new agar, undermining Beijerinck's idea of the *contagium vivum fluidum*. Ivanowsky also tested for infectivity in new and old agar,

[178] Beijerinck, "Concerning a Contagium Vivum Fluidum," 35.
[179] Beijerinck, "Concerning a Contagium Vivum Fluidum," 35.
[180] Beijerinck, "Concerning a Contagium Vivum Fluidum," 36.

finding that infectivity only diffused through older agar, and analogizing from the India ink diffusion studies began to reinterpret Beijerinck's work to indicate a *contagium vivum fixum* – a discrete, particulate agent in suspension. Ingeniously, he carried out prolonged filtrations through Chamberland filters over 36 hours and found that the initial filtrate was infectious but not the later aliquots. From this, he deduced the particulate virus had gradually clogged the pores and inhibited its own filtration over time (probably why Mayer's filtrate was not infectious). Years later, Ivanowsky was able to summarize his findings: "the experiment with the diffusion into agar and especially the fractionated filtration clearly indicates that we are dealing with a *contagium fixum*."[181]

Despite appearances to the contrary, the purpose of including this rather complicated exchange of experimental ideas and techniques between Ivanowsky and Beijerinck is not meant to confuse the reader. Rather, it is meant to show that Ivanowsky's adoption and modification of Beijerinck's diffusion method is a classic case of the spread of scientific knowledge created in one laboratory to another where it was altered and improved by the addition of the India ink model to simulate particulate behavior. It also corroborates Eric Scerri's view that "science proceeds by almost imperceptible small steps in an evolutionary fashion not so much through the genius and brilliance of individual scientists but more by a process of trial and error, chance and sheer stumbling around."[182] The real importance of Ivanowsky's conclusion that the agent was a *contagium fixum*, rather than Beijerinck's *contagium fluidum*, is that it testifies to the successful continuation of a scientific dialogue. Additionally, however,

[181] Lechevalier, "Ivanovski," *Bacteriological Reviews*, 140.
[182] Scerri, *Seven Scientists and a New Philosophy of Science*, 4-5.

even if it did not immediately settle any uncertainties about the agent in question, it indicated that the virus was more than simply a soluble molecule.

Also, the fact that Beijerinck could infect an almost infinite number of plants with solution derived from a plant infected by only a minute amount of this sterile fluid led him to "the conclusion that the contagium, although fluid, reproduces itself in the living plant."[183] Modern commentators generally point to this as the beginning of an understanding of viral reproduction within host tissues, an understanding that was fundamental to the early conceptualization of the virus. Thus, it was coming to be defined by numerous factors. First, it was invisible with light microscopy. Second, it was filterable. Third, it was resistant to known techniques of culture on artificial media. And fourth, it seemed to reproduce itself within the tissues or cells of a host organism.

However, while this last factor was just beginning to be appreciated among these chemists who were investigating plant diseases, it was not really new knowledge in a more general sense. In its 1868 edition, *Chambers's Encyclopedia* had already discussed the "faculty which the human body possesses of generating to an enormous extent the poison of the same nature as that by which the disease was originally produced."[184] Though it cited two contemporary medical texts (*On Morbid Poisons* along with *Science and Practice of Medicine*) as authoritative on this point, the encyclopedia was primarily a compendium of general (rather than specifically medical) knowledge written for the literate public. Still, even though the concept of the disease agent replicating itself in the afflicted host was not completely new in the last few years of the nineteenth century,

[183] Beijerinck, "Concerning a Contagium Vivum Fluidum," 35.
[184] Anonymous, "Virus," in *Chambers's Encyclopedia: A Dictionary of Universal Knowledge for the People*, vol. IX (London: W. and R. Chambers, 1868), 810.

Beijerinck's work probably constituted the first truly experimental work confirming what seemed to be widely accepted general knowledge. Scientific knowledge was already fragmenting into distinct disciplines unintentionally creating barriers to the dissemination of new knowledge., and the conscious circulation of knowledge through scientific communication, dialogue, and debate became increasingly important.

Recall that although both Beijerinck and Mayer had noted that only young, growing tissues in the tobacco plant were affected by the viral contagium (while the mature tissues were immune to its effects), it was the plant physiologist, Beijerinck who made the important deduction:

> … the virus in the plant is capable of reproduction and infection only when it occurs in the cell tissues that are dividing, while not only the mature, but also the expanded tissues are unsuitable for this. Without being able to grow independently, it is drawn into the growth of the dividing cells and here increased to a great degree without losing in any way its own individuality in the process … no ability or reproduction outside of the plant could be proved.[185]

Beijerinck then tried without much success to make some sense of this by forming analogies with other types of plant pathology. Nevertheless, this observation and its interpretation has led most later commentators to credit him with the discovery of viral reproduction within host cells despite the fact that it was hinted at in an encyclopedia three decades earlier with respect to human diseases, albeit without reference to intracellular reproduction. However, there was still confusion about whether the 'viral' agent was a living organism or not.

[185] Beijerinck, "Concerning a Contagium Vivum Fluidum," 38-9.

Erwin Baur (1876-1933) was trained, as was Robert Koch, as a medical doctor, though he soon switched to botany in which he obtained a second doctorate.[186] Examining the understanding of pathogenic organisms at the turn of the century, he confused the issues somewhat. He noted that over the course of the last decades of the 19th century, various microorganisms had been identified as the leading cause of infectious diseases. Moreover, he cited dogmatic assertions that if no etiologic agent had yet been identified for an infectious disease, then a living microorganism similar to those already known was the most likely explanation.

In fact, wrote Baur, "most pathologists who have considered this question from a theoretical point of view … say that only living organisms are at all conceivable as causative agents of infectious diseases."[187] This understanding of infectious pathogens was based on the realization that, as Beijerinck had argued, even a very small amount of infectious material from a single infected human can multiply and spread among thousands of other individuals, the obvious example being smallpox. This being the case, Baur continued to argue the dogmatic position, "the virus of an infectious disease must multiply in the body of the diseased animal," and only living organisms possess the ability to reproduce and multiply their numbers.[188]

Even in the case of a bacterial toxin, such as diphtheria toxin, there was necessarily an underlying bacterial infection leading to the production of the toxin. Thus, it was reasonable to conclude that the pathogenic agent must multiply in the body of

[186] James Johnson, "Erwin Baur," in *Phytopathological Classics: number 7,* translated by James Johnson (Ithaca: Cayuga Press, 1942), 53.
[187] Erwin Baur, "On the Etiology of Infectious Variegation," (1904) in *Phytopathological Classics: number 7*, translated by James Johnson (Ithaca: Cayuga Press, 1942), 57.
[188] Baur, "On the Etiology of Infectious Variegation," 58.

infected individuals, be they humans, animals, or plants. Furthermore, "a pure chemical substance … able to assimilate foreign substances, in order to rebuild itself from them … is yet unknown to us."[189] So, argued Baur, it must be a living organism that causes any infectious disease in which there is multiplication of the infectious agent.

After setting up this apparently reasonable and widely accepted hypothesis, however, Baur went on to argue that in the case of at least one particular infectious disease causing variegation in certain plants (*Abutilon* or Malvacea), the agent cannot be a living organism, because it can only be spread to a healthy plant through grafting. It is certainly infectious because "the grafting of a single leaf … can infect another plant."[190] Crucially, though, no other means of transmission had been discovered. Baur reckoned that if the only means of transmission is through artificial grafting, unknown with this species before 1868, and the putative organism has no other means of dissemination, then it does not qualify as a living organism. It cannot, by itself, infect another plant; it must be transmitted by the act of grafting; it has no independent existence, and cannot have existed before 1868. In the context of early twentieth-century knowledge about infectious organisms, Baur's reasoning was consistent and reasonable. It does not take into consideration such things as the creation of new species or the mutation of species, but those concepts were not universally understood or accepted then.

Thus, for Baur, there must be an error in the theory that led to the "dogma that an infectious disease without a living organic (organized) cause is inconceivable."[191] For example, it is conceivable that the agent of disease may be a metabolic product of the

[189] Baur, "On the Etiology of Infectious Variegation," 58.
[190] Baur, "On the Etiology of Infectious Variegation," 58.
[191] Baur, "On the Etiology of Infectious Variegation," 61.

diseased host that is not a living organism, but could affect, and infect, another organism if grafted onto it. By invoking this single example, Baur calls into question the belief that all infectious diseases must result from infection with living organisms. This is crucial for Baur, because, he says, "a whole series of infectious diseases is known where all our knowledge to date contradicts organisms as a cause."[192] Moreover, the example he gives for this statement is "above all, the mosaic disease of tobacco."[193]

Thus, it is safe to say that in 1904 the conceptualization of the virus as agent of disease was not well worked out, at least not to everyone's satisfaction. It was certainly distinguished from bacteria by its much smaller size, which made it invisible to microscopists and also allowed it to pass through filters that trapped bacteria.[194] But, according to some scientists it seemed to be a toxin, to others a soluble living agent – a *contagium vivum fluidum* or (to Ivanowsky) a *contagium vivum fixum*. To yet others it was not a living organism at all. For example, the investigations of Beijerinck seemed to indicate that viral reproduction took place within living tissues, as though viruses could not reproduce on their own. For the most part, the agents of certain diseases were simply characterized by what they were not: they were not visible, could not be cultivated, or removed from solution. These negative characteristics, however, were very far from a useful description of their structure, their appearance, their chemical composition, or whether they were living organisms, as opposed to simple molecules.

As if this were not enough to confuse the situation, there were two scientists working independently, one in the United States and the other in Germany, who were

[192] Baur, "On the Etiology of Infectious Variegation," 62.
[193] Baur, "On the Etiology of Infectious Variegation," 62.
[194] Collard, *The Development of Microbiology*, 161.

well aware of the work of Mayer, Ivanowsky, Löffler, Beijerinck, and Baur but, nevertheless, concluded, in the last two years of the century, that TMD could be the result of a single enzyme. Albert Woods, in America, reproduced the disease in healthy plants by injecting a peroxidase enzyme. Moreover, peroxidase also diffused well in agar. It also lingered in, and contaminated, soil for some time as well. It, therefore, acted very much like the pathogenic organism described by the European scientists. So, in 1899, Woods considered the infectious agent to be an enzyme; enzymes, of course, are proteins. Kurt Heintzel, in Germany, repeated and corroborated much of the work of Mayer, Ivanowsky, and Beijerinck in 1900. Nevertheless, he came to a distinctly different conclusion based on his own research and efforts to characterize an enzyme from diseased plants. He concluded that the pathogen could be solely a protein functioning as an enzyme, an oxidase, much as Albert Woods had independently concluded.[195]

Interestingly, the writings of these last two scientists are not often discussed in historical discussions of these early disease processes. However, they certainly foreshadowed Stanley Prusiner's late twentieth-century belief that the infectious agent of the TSEs is an infectious protein. Most early twentieth-century accounts simply suggested that the confusion and debate about the actual nature of viruses would continue for decades, which was true until the electron microscope made them visible and empirically accessible. On the other hand, however, in some ways the discussion continues to the present day in the debate about slow viruses and prions, the latter being conceived of as purely proteinaceous particles responsible for infections.

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[195] Hughes, *The Virus: A History of the Concept*, 69-72. Hughes gives a very lucid account of the work of these two and refers to their views as the non-microbial concept of the virus.

As early as the second decade of the twentieth century, then, scientists had begun to define a virus as a filterable and ultramicroscopic pathogen causing disease in plants, bacteria, animals, and humans. In some cases (yellow fever, for example) it was even discovered that mosquitos could carry viruses from host to host. Additionally, viruses could cause cancer in animals, would sometimes produce cellular inclusion bodies in affected tissues, and could only be cultivated by special means in a fertile hen's egg.[196] In 1940, however, the *Lancet* was still attempting to clarify the term:

> Every agent of a transmissible disease will be called a virus (*sensu lato*); there are two sorts of virus, (1) viruses that can be seen with the microscope, and these are called microbes; … (2) viruses that cannot be seen with the microscope, … called according to the rules of priority, contagia.[197]

For many decades of the twentieth century, the term virus remained imperfectly defined, and viral diseases were only poorly understood. In one sense, viruses were defined by what they were not: they were not captured in filters, and they were not visible.

Perhaps the most important aspect of the work done by these early, forerunners of virology is the way they seem to have carried on a written dialogue on the subject of the infectious agent that was being called a virus. They did not necessarily agree with one another. On the contrary, they often disagreed, but they continued a tradition of discourse going back to the Hippocratic authors. They presented their findings and ideas in an open forum that invited discussion, dispute, and debate. The fact, for example, that Ivanowsky had little or no influence on other virologists such as Löffler (or the American, Walter Reed) was probably not due to lack of interest or effort. Rather, it was likely due to his

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[196] Collard, *The Development of Microbiology*, 160-3.
[197] Quoted in OED, online (*Lancet* 3 August 1940: 141/1) http://www.oed.com/view/Entry/223861?redirectedFrom=virus#eid accessed October 31, 2016.

dogged adherence to the belief in a bacterial agent causing tobacco mosaic disease while others were moving beyond this conceptualization to another type of entity entirely.[198]

[198] Lechevalier, "Ivanovski," *Bacteriological Reviews*, 143-4.

Chapter 3:

Scrapie and the Slow Virus, 1898-1958

Scrapie is an affliction of sheep; the name is derived from the tendency of infected sheep to scratch and scrape their skin, damaging their fleece. This descriptive designation has been used in Britain since the middle of the 19th century. Other regional names have also included terms meaning to tremble or trot because of the abnormalities of ambulation and musculature that ensue. As with the early observation of most diseases, then, the initial understanding of scrapie was predicated on the observed symptoms or signs. In a very elementary way, prior to the 1890s, scrapie was initially conceptualized as a scratching or staggering disease of sheep usually with associated trembling. Though based on observation, this conceptualization was more socially constructed and based on local folk knowledge and beliefs; it was not scientifically constructed knowledge.

Probably the earliest clear delineation of scrapie is found in the German literature dating from 1750.[199] It describes the stricken animals' abnormal, trotting gait and their inability to ambulate without difficulty followed by a slow but certain demise.

[199] This is quoted in two histories, Kurt Schneider et al, "The Early History of the Transmissible Spongiform Encephalopathies Exemplified by Scrapie," *Brain Research Bulletin* 77 (2008): 343-355. The other is: Paul Brown and Raymond Bradley, "1755 and all that: A Historical Primer of Transmissible Spongiform Encephalopathy," *British Medical Journal* 317 (December 1998): 1688-1692, though the latter dates it to 1759. However, Schneider acknowledges other scholars, including Gajdusek, who suggest earlier references, even going back to ancient Rome, but such claims are without proper citations. Lacking reliable citations, Schneider discounts all of these older authorities.

Importantly, even at this early date, some observers noted, "this disease is contagious and can cause great damage to the flock."[200] The usual advice was to remove the infected creatures from the flock. Shepherds were advised to butcher infected animals for the table before the animal became moribund and severely wasted. Although the lamb was thought to be safe for human consumption, this belief was somewhat qualified by the injunction to serve it to peasants and servants rather than the noble owners of the flock.[201] This latter admonition suggests that, at the very least, there must have been some suspicion of the quality, if not the actual safety, of the meat. This concern would not be fully realized until the late twentieth century when parts of diseased sheep likely infected British cattle causing BSE.

Many authorities connected the arrival of scrapie in Britain with the importation of Spanish Merino sheep and noted the tendency of breeders to keep its presence hidden if found among their own stock. Knowledge of its presence within a particular flock seriously compromised that breeder's opportunities for selling ewes or hiring out his rams for breeding purposes, and these socioeconomic factors likely slowed any effort to better understand the disease and inhibited a more scientific understanding of it.[202] During the eighteenth century, British sheep suffering from scrapie did not show the pruritus, which became their characteristic symptom during the next century. This itching developed in the following century and led to the British terms scrapie and rubbers, alluding to the

[200] Schneider et al, "The Early History of the Transmissible Spongiform Encephalopathies Exemplified by Scrapie," 345.
[201] Paul Brown and Raymond Bradley, "1755 and all that: A Historical Primer of Transmissible Spongiform Encephalopathy," 1688, and Schneider et al, "The Early History of the Transmissible Spongiform Encephalopathies Exemplified by Scrapie," 345.
[202] Sir Stewart Stockman, "Scrapie: An Obscure Disease of Sheep," *Journal of Comparative Pathology and Therapeutics* 26 (1913): 317-319.

proclivity of infected animals scratching and rubbing their hides to the point of stripping away their wool. The trembling and trotting variety, on the other hand, seemed more prevalent in Germany and France as reflected in their respective nomenclature: *traberkrankheit* and *la tremblante*. When British authors began noting pruritus as the dominant symptom during the first decades of the nineteenth century, they began consciously distinguishing between what they believed to be two varieties of the disease; authorities also began to debate whether scrapie was infectious or hereditary.[203] One British commentator noted in 1811, that a very long incubation period of up to two years was known as early as 1745.[204]

German authors disagreed about whether the different symptoms of rubbing or scraping on the one hand and difficulty walking (trotters) on the other hand represented two different diseases. The German writer, Georg May, alluded to its sporadic occurrence while others invoked heredity, or a possible hereditary predisposition.[205] So, from the eighteenth and nineteenth centuries there was already considerable confusion over whether the disease in sheep was contagious, hereditary, or simply occurred sporadically.

May also referred to unsuccessful efforts by nineteenth-century German scientists to transmit scrapie from one animal to another.[206] This was probably the first attempt at

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[203] J.P. McGowan, *Investigation into the Disease of Sheep Called "Scrapie" (Traberkrankheit; La Tremblante): with especial reference to its association with Sarcosporidiosis* (Edinburgh: William Blackwood and Sons, 1914), 2-11.
[204] McGowan, *Investigation into the Disease of Sheep Called "Scrapie,"* 1.
[205] McGowan, *Investigation into the Disease of Sheep Called "Scrapie,"* 13-20. McGowan seems to have translated May's 1868 work acknowledges quoting "practically the whole article" in his own monograph.
[206] McGowan, *Investigation into the Disease of Sheep Called "Scrapie,"* 20 and 24. McGowan notes that German veterinary textbooks of the late 19th century considered, with sound reasoning, an infectious etiology more likely than hereditary transmission.

experimental transmission and indicates it was thought to be an infectious disease. This attempt to link scrapie to the germ theory of disease likely marks the early beginnings of attempts at creating scientific knowledge about the disease. May, however, rejected the possibility that the disease was contagious, preferring instead to implicate hereditary factors provoked by overbreeding and inbreeding.[207] Another German author, Cassier, noted the existence of sarcosporidial cysts in the muscles of affected animals, but considered this an incidental finding too common in otherwise healthy animals to be of any importance.[208] He concluded rather emphatically that "even by a very exhaustive exact microscopic examination of the whole nervous system." nothing pathognomonic (diagnostic of, and/or specific to, a particular disease) could be found in cases of scrapie.[209]

At the very end of the nineteenth century, a pair of French investigators, Besnoit and Morel, adopted the very rigorous scientific methods of Rudolf Virchow: searching for the pathological abnormalities of diseased organs within the actual cells of, for example, the nervous system. The Frenchmen alluded to research by seven of their predecessors, all of whom came to contradictory conclusions about the microscopic pathology of scrapie in the brain. Some found inflammation; others found edema and hemorrhage. Essentially all found pathology in different locations of the central and

[207] McGowan, *Investigation into the Disease of Sheep Called "Scrapie,"* 17-20.
[208] McGowan, *Investigation into the Disease of Sheep Called "Scrapie,"* 22. McGowan emphasized Cassirer's repudiation of a sarcosporidial etiology, because he (McGowan) would go on to implicate these organisms as causative agents of the disease.
[209] Quoted in McGowan, *Investigation into the Disease of Sheep Called "Scrapie,"* 22.

peripheral nervous system. But, there was no consistency to their findings and no mention of any efforts to determine the etiology of scrapie.[210]

Consequently, Besnoit and Morel resolved to enter into this dialogue and set the record straight, at least as far as the pathological examination of the brain was concerned, and they actually did so. Even though subsequent research failed to corroborate the pathological lesions they located in the peripheral nerves of the limbs and the body, they were certainly the first to describe the now accepted hallmark of neuronal vacuolization in brain tissue: "the nucleus is pushed to the periphery of the cellular protoplasm to make room for vacuoles, more or less voluminous."[211] Their 1898 publication even includes very clear photomicrographs of the vacuolar disruption of neurons and marks the first, explicitly scientific, knowledge about scrapie.

Despite providing new and important histological information about scrapie, Besnoit and Morel were unable to add any knowledge to the possible etiology of the disease: "bacteriological investigations gave us only negative results … we were never able to substantiate the presence of micro-organisms."[212] Like the German scientists who tried to transmit scrapie, the French researchers were certainly suspicious that it was an infectious illness but could find no corroborating microscopic evidence. They concluded, in fact, that the disease must result from poisoning or a toxin, probably internalized through an oral route; they did not attempt experimental transmission to healthy animals.

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[210] Besnoit and Ch. Morel, "Note sur les Lésions Nerveuses de la Tremblante du Mouton," *Revue Vétérinaire* 23 (1898): 397-398.
[211] Besnoit and Morel, "Note sur les Lésions Nerveuses de la Tremblante du Mouton," 399; my translation.
[212] Besnoit and Morel, "Note sur les Lésions Nerveuses de la Tremblante du Mouton," 400; my translation.

Even so, Besnoit and Morel began an essential scientific dialogue between French and British scientists that would eventually yield crucial information about the transmissibility and etiology of scrapie. Across the channel from Besnoit and Morel, a trio of scientists kindled the British tradition of scrapie research.

England

Sir Stewart Stockman delivered a lecture about scrapie to English breeders in 1913 and included the findings of his own historical research, associating the arrival of scrapie in Britain with the arrival of sheep from Spain. While earlier continental authorities, said Stockman, noticed its predilection for certain flocks and believed it to be hereditary, in Britain most authorities had concluded it was contagious as early as the late eighteenth century and instituted the only effective remedy: "rigorously destroying all the affected animals."[213] All authorities, however, concluded the disease was limited to sheep, did not spread to other species, and the meat of the animals was safe for human consumption. Stockman worked closely with an equally eminent, though older, veterinary surgeon, Sir John McFadyean, who was, in fact, the younger man's father-in-law. Both men came from humble backgrounds; earned knighthoods for their substantial contributions to scientific knowledge; and shared a very close personal and professional relationship.

McFadyean was such a dedicated scientist and veterinarian that, while he was a professor of veterinary medicine, he simultaneously attended medical school largely in order to obtain a better understanding of the new and developing germ theory of

[213] Stockman, "Scrapie: An Obscure Disease of Sheep," 319.

diseases.[214] It was probably not coincidental that McFadyean's interest in bacteriology developed and matured at the same time Koch and Pasteur were making great discoveries; he was fascinated by the new germ theory that was simplifying so many formerly incomprehensible aspects of disease causation. Germ theory was literally a new paradigm, and was rapidly replacing the older, humoral paradigm. McFadyean was a devoted convert to the new paradigm; medical school imprinted germ theory into his scientific understanding of disease etiology, and he was primed to see scrapie in light of its principles.

Like his father-in-law, Stockman was also a committed scientist He was so dedicated and industrious that his obituary hinted that his devotion to work probably contributed to his early death. [215] The younger man was a firm believer that the most important aspect of a scientific education was the self-directed work done after a formal education along with a willingness to communicate with other scholars, "which means that a man is trying to work out things for himself, paying full attention, of course, to what others are doing."[216] For Stockman, real scientific progress required objective study *and* an understanding of what knowledge other scientists were creating.

J. P. McGowan, whose scholarly translations provided so much historical information about scrapie in Europe, was also a researcher who presented his own

[214] Iain Pattison, *John McFadyean: A Great British Veterinarian* (London: J.A. Allen, 1981), 44.
[215] Anonymous, "Sir Stewart Stockman, M.R.C.V.S," *British Medical Journal* 1, issue 3414 (June 12, 1926): 1017. See also, Anonymous (presumably Sir John McFadyean), "The Late Sir Stewart Stockman," *Journal of Comparative Pathology and Therapeutics* 39, no. 2 (June 30, 1926): 164-165.
[216] Sir Stewart Stockman, "Letter to Major General Frederick Smith," (February 16, 1920), folder 'fs/3/2/49' in the Royal College of Veterinary Surgeons, London, England: page 2. Accessed August 01, 2017.

experiments and theories, along with the historical information, in his 1914 monograph. McGowan actually acknowledged Stockman's 1913 article in order to establish that his own monograph took priority over Stockman's lecture: "To prevent possible misunderstanding, it may be stated that the chapters dealing with the history of the disease in Great Britain and elsewhere were completed prior to any public discussion of this aspect of the subject."[217] There was likely an element of rivalry between McGowan, on the one hand, and the McFadyean – Stockman duo, on the other. Notably, they completely disagreed about the etiology and nature of scrapie.

Kiheung Kim discusses the work of these British scientists, but he is more concerned with stressing their dependence "upon observational reports from farmers and shepherds" and downplaying their scientific work.[218] Kim focuses heavily on the social construction of knowledge and is more concerned with "the driving force for investigation by local demands [that played] an important role in developing the concept of scrapie … [and] played an important role in establishing research institutes."[219] This focus on institutional settings suits his sociological interpretation better, but it is not the complete story. As we shall see, for example, these three scientists carried out numerous scientific experiments in addition to obtaining accurate epidemiological evidence from reliable observers in order to develop well-conceived theories.

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[217] McGowan, *Investigation into the disease of sheep called "Scrapie,"* vi. Although the French scientist and author, Maxime Schwartz notes that McGowan was also a knight and known as Sir John Poole McGowan, this was not apparent in my researches; see Schwartz, *How the Cows Turned Mad*, 27.
[218] Kim, *The Social Construction of Disease: From Scrapie to Prion*, 20.
[219] Kim, *The Social Construction of Disease: From Scrapie to Prion*, 20.

McGowan was a medical doctor, not a veterinarian; but like many other physicians at the time, he wrote about diseases of animals and compared them to human maladies.[220] Moreover, it was common for British authorities to enlist the help of medical doctors with epizootics and difficult diseases of animals, much to the embarrassment and dissatisfaction of the British veterinary profession, which often considered itself slighted. It is unlikely that Stockman and McFadyean appreciated the assistance of McGowan with this veterinary problem, which they were well equipped to handle alone.

McGowan's historical research brought together the work of German and French authorities who believed that the disease was not contagious but had a hereditary component. He particularly emphasized the German scientist, Cassirer's findings of sarcosporidial cysts in affected animals, notwithstanding Cassirer's own dismissal of their importance. Moreover, McGowan corroborated these findings with his own autopsy work.[221] Additionally, he did experimental research. Injecting rabbits with sarcocystin, a toxin isolated from sarcosporidia, he believed he had provoked, in his experimentally 'infected' rabbits, the itching and scratching so characteristic of scrapie affected sheep.[222]

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[220] McGowan, for example, was very interested in Rous' work dealing with the causation of sarcomas in fowl and the relationship between anemia in pigs and the green sickness or chlorosis of young human females. See J.P. McGowan, "Iron Deficiency and its Possible Relationship to Human Disease," *Lancet* 204, no. 5282 (November 22, 1924): 1060-1061 and J.P. McGowan, "Causation of Cancer," *The British Medical Journal* 1, no. 4029 (March 26, 1938): 698-699. See also, Michael Worboys, *Spreading Germs: Disease Theories and Medical Practice in Britain, 1865-1900* (Cambridge: Cambridge University Press, 2000), 43-72.

[221] McGowan cites this investigator as follows: Cassirer, Ueber die Traberkrankheit des Schafes: Virchow's Archiv, 1898. Bd. CLIII. p. 89.

[222] McGowan cites these investigators as follows: Pfeiffer. Die Sporoz. als Krankheitserreger. 1892. Janin. Archiv de Parasit. 1906-7. XI. p. 233.

Even though sarcosporidia were known to be common in otherwise healthy animals and thought to be a coincidental and harmless finding, McGowan believed that poor breeding practices led to an overwhelming concentration of the sarcosporidial parasite that produced scrapie as the animals aged. Putting all of the historical and empirical evidence together, McGowan elaborated his theory of causation: poor breeding practices led to a pernicious concentration of an otherwise harmless parasite, sarcosporidia, and its toxin, sarcocystin, which produced the fatal affliction, scrapie. He also believed that the sarcosporidia might, or might not, be passed across the placenta to unborn lambs: "a healthy ewe may give rise to a scrapie lamb; and a scrapie ewe to a healthy lamb."[223] McGowan believed that the "real determinant for the disease [was] this method of breeding, and given a healthy stock," poor breeding would allow "automatically, or as one might say, 'de novo,' heavy sarcosporidial infections [to] develop and scrapie appears."[224] For McGowan, then, scrapie appeared sporadically but not randomly; it was caused by poor breeding.

So, at the end of the nineteenth century and the beginning of the twentieth, scrapie was a disease understood to be confined to sheep, generally older than eighteen months. It manifested as an itch, or pruritus, initially causing affected animals to scrape or rub their hides and progressing rapidly to death in a few months. The two accepted methods of coping with the disease were slaughtering young sheep for sale as mutton before the disease developed and, in the case of older, symptomatic animals, eradicating the entire herd. However, the British authorities were divided over the likely etiology; Stockman and McFadyean disagreed with McGowan about the importance of poor breeding and

[223] McGowan, *Investigation into the Disease of Sheep called "Scrapie,"* 108.
[224] McGowan, *Investigation into the Disease of Sheep called "Scrapie,"* 108-109.

sarcosporidial infestation in the genesis of the disease. Everyone, however, agreed the disease was limited to sheep, did not spread to other species, and the meat of the animals was safe for human consumption.

Despite the fact that researchers were unfortunately "in possession of very few experimental facts, and [were] forced to draw deductions from accumulative circumstantial evidence," Stockman believed that one could "speculate rationally regarding the epizootiology of the disease, and even to arrive at conclusions regarding its nature."[225] For example, he was able to locate a husbandman who had never been troubled by scrapie until buying one- to two-year-old ewes for breeding; though quite healthy when purchased, several of these ewes developed scrapie after copulation. The breeder quickly slaughtered or sold all of the imported sheep along with their lambs to rid his flock of the disease. Notwithstanding these efforts, the disease appeared about eighteen months later among his original stock, which had no genetic connections to the imported animals. From this breeder's experience, and after discarding alternative explanations, Stockman concluded scrapie must be contagious.

It was not at all clear, though, how the disease might be passed from one animal to another. It might be transmitted from ram to ewe, or vice versa, during mating. It might be passed across the placenta from ewe to lamb during gestation. Or, Stockman presciently observed, it might be "transmitted from animal to animal by association at pasture."[226] Stockman developed an almost neo-miasmatic theory of transmission. In an epistolary discussion of an outbreak of foot and mouth disease among cattle, for example,

[225] Stockman, "Scrapie: An Obscure Disease of Sheep," 322.
[226] Stockman, "Scrapie: An Obscure Disease of Sheep," 324.

he wrote to another veterinarian, "we know for a fact that the infection can be carried a long distance by the wind. I have myself, in common with others, actually seen the thin saliva whirled up in the air, out of sight, and I have afterwards found outbreaks some miles away, in the direction in which the wind was going and found no other connection between the second and first outbreak."[227] This was not mere speculation; it was rational theorizing from the observed evidence of aerosolized saliva and downwind propagation of the disease.

Even so, Stockman did not believe that scrapie could be transmitted from animal to animal in enclosed stalls or stables, though he considered it "undoubted fact that animals, long before they have shown clinical signs of scrapie, and even those which never shown such symptoms, may give rise to affected progeny."[228] He knew of no evidence of fever during the disease, and he also insisted that it was a mistake to believe scrapie to be inevitably fatal, because he had personally "seen several severe and typical cases of scrapie recover, under his eye."[229] Stockman noted the presence of vacuolization of certain neurons within the brain and spinal cord but did not emphasize it even though he knew of the findings of Besnoit and Morel. On the other hand, he pointed out cytoplasmic inclusion bodies within neuronal cell bodies of the spinal cord, which he

[227] Stockman, "Letter to Major General Frederick Smith," (February 16, 1920), folder 'fs/3/2/49' RCVS, page 3-4. At the end of this typed communication, Stockman added, in his own hand, that numerous cases of the disease were appearing on farms where nothing considered contagious had been "brought onto the farm."
[228] Sir Stewart Stockman, "Contribution to the Study of the Disease Known as Scrapie," *Journal of Comparative Pathology and Therapeutics* (1926), vol. 39: 42-71, 46.
[229] Stockman, "Contribution to the Study of the Disease Known as Scrapie," 46. Stockman sometimes wrote of himself in the third person singular. See pages 57-59 for details of five cases of scrapie that he witnessed recover completely.

never found in sheep without scrapie.[230] The "possibility that they denoted the presence of a virus led" Stockman to carry out unsuccesful experimental inoculations with emulsions of infected brain tissues.[231]

Stockman also inoculated healthy sheep with the sarcosporidia derived from scrapie-infected sheep to evaluate McGowan's claims and found no evidence sarcosporidia was involved in scrapie. He tried various treatment regimens, also without any success. Nevertheless, the drugs he chose were interesting: "the newer organic compounds of arsenic, the aniline dyes, etc."[232] He does not discuss it, but his choice of drugs is certainly reminiscent of the investigations of Paul Ehrlich in Germany, especially since he actually included a trial of Salvarsan, Ehrlich's revolutionary drug for the treatment of syphilis. He was almost certainly influenced by Ehrlich's work, and he thereby, at least indirectly, brought the great German chemotherapeutic scientist into the ongoing international dialog about scrapie.

In answer to those who still believed the disease was hereditary, Stockman pointed out "that no disease is known which is both hereditary and contagious, although the mistake is not unnatural in a lay mind which does not always distinguish the difference between hereditary transmission and congenital infections."[233] Likewise, in 1878, French veterinary scientist, François Tabourin had vociferously denied the possibility that transmissible diseases, such as rabies, could also develop spontaneously, as they were often thought to do: "In our view, contagion and spontaneity are two

[230] Stockman, "Contribution to the Study of the Disease Known as Scrapie," 52-56.
[231] Stockman, "Contribution to the Study of the Disease Known as Scrapie," 56.
[232] Stockman, "Contribution to the Study of the Disease Known as Scrapie," 60.
[233] Stockman, "Scrapie: An Obscure Disease of Sheep," 323.

irreconcilable things … our mind refuses to accept the birth of a specific [transmissible] disease without the original involvement of its necessary seed."[234] These were very prophetic observations and ones that still vex researchers today who believe that certain spongiform encephalopathies, which are thought to occur sporadically, are known to occur through hereditary transmission and by infectious transmission.

In any event, Stockman knew there was no treatment, and the only effective remedy was complete eradication of an infected flock. Fresh, uninfected stock could later be reintroduced, because pastures did not remain contagious for long. However, like earlier, nineteenth-century shepherds, he advocated slaughtering suspected animals in order to salvage their meat: "Affected sheep on the first indication of the disease should be slaughtered … in the early stages the sheep may make a fairly good butcher price, whereas they will make less the longer they are kept."[235] Amazingly, even in the twentieth century, in light of the germ theory of disease, and dealing with a disease he thought to be contagious there was no apparent concern for communicating the disease to humans through consumption of infected meat. This was undoubtedly because there had never been any known transmission of disease between affected sheep and humans. It was simply inconceivable considering the common knowledge of its history.

In his 1913 lecture, Stockman made a very intriguing conjecture that, in light of our present knowledge, initially seems to have been mistaken:

> … although scrapie is looked upon as an affection which always ends fatally … It is quite possible, even probable, that a considerable number of sheep on an

[234] Quoted in Schwartz, *How the Cows Turned Mad*, 22-23.
[235] Stockman, "Scrapie: An Obscure Disease of Sheep," 326.

> infected farm take the disease and recover from it before it passed to the later stages, when it is easily diagnosable.[236]

However, this was a remarkable and very profound speculation, and whether it is correct or not remains difficult to answer today, especially with respect to the human forms of spongiform encephalopathy.[237]

The Journal of Comparative Pathology and Therapeutics, begun and edited by McFadyean, exemplified the ongoing scientific debate between McGowan and McFadyean. In June of 1918, Sir John wrote an article criticizing McGowan's theories about the etiology of scrapie. Six months later, the December issue contained McGowan's rebuttal, immediately followed by McFadyean's reply. In the June article, McFadyean outlined, "probable facts with regard to the disease as it occurs in [Britain] and [discussed] the principal views that have been advanced as to its cause," and

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[236] Stockman, "Scrapie: An Obscure Disease of Sheep," 325.

[237] It is suspected, for example, that there are asymptomatic carriers of vCJD. A study published in 2013 revealed that one out of two thousand human appendices in Britain contained the abnormal prion protein characteristic of vCJD infection. See, O Noel Gill, Yvonne Spencer, *et al*., "Prevalent Abnormal Prion Protein in Human Appendixes after Bovine Spongiform Encephalopathy Epizootic: Large Scale Survey," *British Medical Journal* 347, no. 7929 (19 October 2013): 11. This prevalence is far higher than the 177 known cases of vCJD in the United Kingdom would indicate and points to a significantly higher level of subclinical vCJD in the British population than was otherwise suspected. Perhaps individuals with more resistance to the disease may still be susceptible to acquiring, and hosting, the pathogen without actually coming down with manifestations of the disease itself. That is, they may be immune to the disease but vulnerable to acquisition and dissemination of the pathogen. Therefore, even though he was certainly not considering any extension of scrapie (or a scrapie-like disease) to humans, Sir Stewart Stockman may have been unusually intuitive, even insightful, in postulating the existence of an asymptomatic carrier state in 1913.

presented the results of his own experiments.[238] Noting the long incubation period of scrapie and its predilection for large, hillside pastures, he hinted at the importance of pastures in the transmission of the disease. He pointed out the higher incidence in certain types of sheep but attributed this species specificity to the distribution of species in England rather than to any inherent qualities of the disease or the different ovine species. He cautiously created a detailed analysis of the contemporary understanding of the disease, carefully detailing what he believed was reliable and what was not. Like McGowan, he acknowledged the differences between the disease in Britain and on the continent, "which so long prevented recognition of the fact that the Continental disease was identical with the one termed scrapie in this country."[239]

Regarding the etiology of scrapie, McFadyean believed "erroneous opinions with regard to the etiology … were often the outcome of a too narrow experience;" people were unfamiliar with others' knowledge.[240] And, the restriction of local knowledge hindered "a wider acquaintance with the disease [which] would have prevented … error by showing that the particular circumstance" was not necessarily the norm.[241] This, of course, was the reason he had founded the *Journal of Comparative Pathology and Therapeutics*: to circulate knowledge through written discourse, improving the conceptualization of disease in general. Carefully parsing the information gleaned from reliable husbandmen, he constructed a cautious etiology: "scrapie is caused by the

[238] Sir John McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics* 31, no. 2 (June 1918): 103.
[239] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 106.
[240] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 108.
[241] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 108.

multiplication of some parasite in the sheep's body, and is spread by the direct or indirect transference of the parasite from the diseased to the previously healthy."[242]

McFadyean then specifically critiqued McGowan's theory, a synthesis of continental opinions and his own experimental work. To be fair though, McGowan's methodology was not unreasonable and his experimental work, though somewhat superficial, was not totally without merit. As a medical doctor, he was certainly familiar with the new germ theory paradigm of disease causation, and he incorporated the sarcosporidial organisms into his conceptualization of scrapie. McGowan's fundamental error, as McFadyean correctly recognized, was relying on the "absence of any condition post-mortem, *except* extensive Sarcosporidiosis, sufficient to or of a nature likely to cause the phenomena observed in the disease."[243] That is, McGowan did not consider alternatives, especially alternatives that were not immediately conceivable to him; his conception of scrapie was confounded by the problem of underdetermination, especially the corollary problem of unconceived alternatives. McGowan, himself, even alluded to the problem of underdetermination, though not by name, in his rebuttal of McFadyean's critique. Dismissing one of Sir John's assertions, McGowan shrewdly asserted, "other quite different interpretations are possible."[244] Both McFadyean and McGowan failed to recognize the problem of underdetermination in their own theories because of their

[242] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 111. McFadyean's use of the word 'parasite' should not be confused with McGowan's identification of sarcosporidia (a parasite in the modern use of that term); instead, McFadyean uses 'parasite' in the more generic, 19th-century sense of 'germ' or 'microbe.'

[243] McGowan, *Investigation into the Disease of Sheep called "Scrapie*," 110-111, (my italics).

[244] J.P. McGowan, "Scrapie," *Journal of Comparative Pathology and Therapeutics* 31, no. 4 (December 2018): 278-290, 279.

seemingly inevitable theory-laden approach to evidence that favored their own preconceptions.[245]

McGowan did not believe scrapie was contagious. Rather, he conceived of it occurring spontaneously when a critical level of sarcosporidial infestation had developed. McFadyean enumerated several cogent objections to this, vociferously maintaining that scrapie never occurs sporadically: "All the known facts … suggest that it is contagious as opposed to sporadic."[246] Nevertheless, the disagreement was fertile, promoting further research and publication. In fact, it does not matter whether either one, or the other, was completely wrong as long as they were still experimenting, analyzing, arguing and trying to determine the best theory to fit the evidence. Scientists have always been, and always will be, wrong on many (maybe most) occasions; worse, even when they are hailed as true discoverers and given prestigious prizes, their work is almost inevitably superseded by some more important and newer 'scientific truth.' It is the scientific method and its scrutiny through debate and unfettered discourse that are important and lasting.

Sir John McFadyean extended the research of his son-in-law by carrying out at least ten experiments several of which involved inoculating a dozen sheep with either blood or cerebrospinal fluid from diseased animals. The animals were watched for at least two years with no evidence of successful disease transmission after oral, subcutaneous, or intravenous inoculations. He was also unable to infect healthy sheep by placing them in contact with diseased animals. Like Stockman, he too, canvased breeders and shepherds

[245] Even from the 21st century, this is a legitimate critique, because both Hume and Pierre Duhem had discussed aspects of the principle of underdetermination well before this dialogue between McFadyean and McGowan.
[246] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 115.

for their observations and deductions derived from experience. Reckoning that scrapie was "contagious as opposed to sporadic, [and] never arises in a previously healthy flock," he stressed "the very long period of incubation" during which the animal is completely asymptomatic and there is no reason to suspect, let alone diagnose, the illness.[247] He even wondered, "whether, as in many other diseases, infection may in some cases be permanently latent."[248] He had certainly incorporated a long observation period into his inoculation experiments; his failure probably had more to do with technique than concept.

Assimilating Stockman's information about the shepherd who inadvertently imported scrapie into his flock and saw it spread to his previously uninfected animals and dismissing the work of McGowan, McFadyean reasoned that "when a disease occurs in enzootic form [and is not due to] breed, climate, diet, and soil … one naturally considers whether … it is parasitic."[249] Recall that German scientists had tried to transmit it. Likewise, Besnoit and Morel had also considered infection likely, but their histologic and bacterial investigations failed to reveal any evidence of microorganisms. Though, the idea of a transmissible pathogenic agent commensurate with the germ theory was not new with McFadyean, he had the medical background and commitment to the germ theory to address it from a different standpoint: making reasoned inferences from empirical and epidemiological data.

[247] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 115 and 103.
[248] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 119.
[249] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 109.

For McFadyean (and presumably Stockman, as well), the cause was an organism spreading from one animal to another, but it did not spread within the confines of a stable or fold even when healthy animals were mingled with the sick. Though usually in agreement, the two men differed in their understanding of contaminated pastures. Stockman proposed that pastures became infected and facilitated the passage of the disease. McFadyean, on the other hand, believed, probably incorrectly, that "an affected farm can be cleared of the disease by selling the infected flock and re-stocking, even if the latter follows immediately."[250]

Nevertheless, while McFadyean and Stockman, seem to have made better inferences that have stood the test of time and are better correlated with our present day conceptualization of scrapie, McGowan's work cannot be dismissed lightly. He researched the work of other scholars in Germany and France; he assimilated those elements of their work he thought most explanatory; he autopsied diseased sheep to see for himself; and he conducted clever experiments with a possible toxin. If nothing else, McGowan was a necessary foil to McFadyean and Stockman; he goaded their egos, spurred their research, and impelled them to more precise conceptualizations of the etiologic agent as a germ with a very long latency that would require special circumstances for experimental transmission.

France and Scotland

Following the work of these researchers, S. H. Gaiger, director of the Animal Researches Laboratory (forerunner of the Moredun Research Institute) in Scotland and a

[250] McFadyean, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 111.

noted scholar of veterinary pathology, summarized the knowledge of scrapie in 1924 and successfully challenged and disputed McGowan's thesis because of new research findings about sarcosporidia.[251] New research had shown that sarcosporidia did not cross the placenta and that, in the United States, ten-fold greater infestations of sarcosporidia than usually found in scrapie-infected victims did not lead to scrapie. Instead, Gaiger conceptualized scrapie as an infectious disease with an incubation period of more than two years and wondered if "there were no limit to the length of the period of incubation" and if "the disease may even lie dormant" but transmissible.[252] He assimilated and discussed the work of McFadyean and asserted that more work needed to be done with inoculation experiments "to determine in which part of the affected animal lies."[253]

Gaiger was either unaware of the work of Besnoit and Morel, or he discounted the importance of their findings of cellular vacuolization. Either way, though, he was pointing the way toward determining if the brain was the site of the pathology. Supposing that it was the likely site of infection, Gaiger prepared a "heavy emulsion of the brain and cord" from infected sheep in an attempt to immunize young sheep against scrapie.[254] He was not successful, but his efforts to use emulsions of affected brain for immunization experiments would be reflected in later French experiments to use similar cerebral emulsions to successfully transmit scrapie to healthy animals. Gaiger also confidently

[251] S.H. Gaiger, "Scrapie," *Journal of Comparative Pathology and Therapeutics* 37 (January 1924): 259-277. See also, Anonymous, "Obituary: Professor S.H. Gaiger, F.R.C.V.S.," *Journal of Comparative Pathology and Therapeutics* 47 (January 1934): 330.
[252] Gaiger, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 266.
[253] Gaiger, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 265.
[254] Gaiger, "Scrapie," *Journal of Comparative Pathology and Therapeutics*, 277.

asserted the reality of the two varieties of scrapie: the scratching variety and the trotting variety on the continent.

Thus, Gaiger, like McGowan, McFadyean, and Stockman before him, was following in the path of the first Frenchmen, Besnoit and Morel. Moreover, the Britons were contributing to an international scientific dialogue about the disease and setting the stage for the work of two more Frenchmen, Jean Cuillé and Paul–Louis Chelle. McFadyean's concept of a very long incubation period, in particular, would begin to take on the role of an anomaly within the germ theory paradigm, and it was crucial in guiding the research of the French who mentioned McFadyean and Stockman by name and knew that McFadyean believed the incubation period could be eighteen to twenty-four months.

This long incubation period had been a major stumbling block for researchers, because it did not fit well into the commonly accepted paradigmatic behavior of already known pathogenic agents, which involved transmission of the microbe followed quite soon by obvious signs of infectious illness with fever and other signs of inflammation. In turn, this was then followed by a period of greater or lesser illness that ran its course over a few days or weeks with the animal either surviving or not. Though a much longer course was probably not totally inconceivable, it was certainly not within the usual parameters of the germ theory and was, therefore, not part of their theory-laden approach to experiments and empirical evidence and from which their theories were developed. Thus, scientists had a difficult time formulating the concept of a slowly evolving disease. Thanks to the suspicions of McFadyean, however, Cuillé and Chelle were able to incorporate into their own preliminary conceptualization of the disease, an element they would not otherwise have investigated. They correctly postulated that earlier failures to

experimentally transmit scrapie might have been due to inadequate length of the observation period after the inoculation.

Using an inoculum of brain or spinal cord tissue, the Frenchmen undertook a series of inoculations into nine sheep. Seven of these died soon after of complications unrelated to the experiment. However, two of the experimental animals did contract scrapie. The first showed signs at fourteen months and died two months later; the second showed signs at twenty-two months and died just over two years after inoculation. The researchers also kept two control animals penned with the sheep, and the controls remained healthy. Thus, they had essentially proven that scrapie was a transmissible disease with a very long latency, or incubation, period. At the same time, the evidence of their control animals remaining healthy in close proximity to the infected sheep suggested that the organism, whatever else it was, was not highly contagious. Because neither they, nor other researchers, had found any evidence of bacteria or other visible pathogens, Cuillé and Chelle followed contemporary scientific thinking and suggested that the agent was likely a virus.[255]

Recall that, despite allowing for a long incubation period, McFadyean had been unsuccessful in his attempts to transmit scrapie. French scientist and historian, Maxime Schwartz, is likely correct when he argues the failure was due to McFadyean's use of blood and spinal fluid, rather than the more infectious emulsions of brain and spinal cord tissue. Interestingly, Schwartz suggests that the French researchers enjoyed the benefit of Pasteur's legacy. Pasteur had used emulsions of brain and spinal cords to transmit rabies,

[255] J. Cuillé and P.-L. Chelle, "La Maladie dite 'Tremblante' du Mouton est-elle Inoculable?" *Comptes Rendus de L'Academie des Sciences*, 203 (1936): 1552-1554.

and Cuillé and Chelle, being Frenchmen, naturally followed his methods. With tongue in cheek, Schwartz attributes "McFadyean's error to his having worked in English while Pasteur" had worked in French.[256]

Two years later, the French scientists published another article repeating and confirming their initial work and also showing that inoculation, using brain tissue from infected sheep, could be successfully done through diverse routes: subcutaneous, intracerebral, epidural, or intraocular. They also successfully transmitted scrapie from one of the two animals they had first infected in order to show that transmission could occur after passage of the mysterious agent through an intermediate host. By this point, they were confident that the incubation period was at least a year and probably closer to two years.[257]

In the same journal and volume, Cuillé and Chelle presented an article describing their use of Chamberland filters to filter the emulsified inoculum used in their original experiments. Recall that this was a common microbial technique of the time done in order to remove any unknown or cryptogenic bacteria.[258] These filters would not allow passage of bacterial sized particles, and, as already discussed, by the beginning of the

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[256] Schwartz, *How the Cows Turned Mad*, 40.

[257] J. Cuillé and P.-L. Chelle, "La Tremblante du Mouton est bien Inoculable" *Comptes Rendus de L'Academie des Sciences*, 206 (1938): 78-79. Part of the reason for repeating their initial experiments was the refusal of several other French scientists to accept their initial results; see, Schwartz, *How the Cows Turned Mad*, 39-42.

[258] See Stuart Mudd, "Filters and Filtration," in *Filterable Viruses*, ed. Thomas M. Rivers (Baltimore, William & Wilkins Company, 1928), 55-61. See also A.P. Waterson and Lise Wilkinson, *An Introduction to the History of Virology* (Cambridge: Cambridge University Press, 1978), 23ff. Chamberland filters were also called Chamberland-Pasteur filters, because Charles Chamberland working in Pasteur's laboratory developed them in 1884. See, C. Chamberland, "Sur un Filtre donnant de l'eau physiologiquement pure," *Comptes Rendus de L'Academie des Sciences*, 99 (1884): 247.

twentieth century, viruses were being defined by the fact that they were filterable: they passed through filters designed to remove bacteria. If the fluid passing through such a filter retained its unfiltered ability to transmit disease, the agent must be too small to be a bacterium. Consequently, it fit into the category of extremely small organisms becoming classified as viruses. Additionally, these very small organisms were too small to be seen with light microscopy. Unseen through the microscope, they were called 'ultramicroscopic.' As early as 1849, for example, South Carolina physician, Samuel Henry Dickson was able to assert that the actual composition of the contagious matter itself, as opposed to simply the fluid from a smallpox vesicle, was "ultra-microscopically minute and imperceptible."[259]

In the early years of the twentieth century, before the advent of electron microscopy, viruses were conceptualized as ultramicroscopic and filterable infectious agents. Admittedly, a soluble toxin was known to pass through filters, because it was literally dissolved in, and part of, the solution. However, passage of the agent through one animal and then passing it to another animal would dilute a toxin, because a chemical toxin could not reproduce itself and maintain its toxicity. Thus, the ability to reproduce themselves within a host animal and remain toxic in serial passages to other animals had become another hallmark of viruses. Cuillé and Chelle had shown that passage from one animal to the next did not seem to lessen the virulence of whatever transmissible agent was causing scrapie, making a virus the likely agent.[260]

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[259] Samuel Henry Dickson, "On Contagion, "*The American Journal of the Medical Sciences* 18 (July 1849): 116.

[260] J. Cuillé and P.-L. Chelle, "La Tremblante du Mouton est-elle Determinée par un Virus Filtrable?" *Comptes Rendus de L'Academie des Sciences*, 206 (1938): 1687.

Just prior to the work of these two Frenchmen, another French scientist, P. Lépine had entered into a parallel dialogue with the British scientists, Pool, Brownlee, Wilson, Greig, and Gordon concerning louping-ill virus, which they had recently shown to be filterable. Lépine received a specimen of "virus of the trembling disease of sheep (louping ill), isolated in Scotland by Pool, Brownlee and Wilson" and noted, "eight preliminary passages "in the brain of the mouse did not diminish its virulence with regard to the sheep."[261] This work illuminates not only the importance of research on viruses at this time but, more importantly, reinforces our understanding of the international role of scientific discourse in the conceptualization of viruses and viral diseases during the early twentieth century.

Cuillé and Chelle tried unsuccessfully to inoculate rabbits and noted, that previously, researchers had been unable to transmit the scrapie agent to other small animals such as mice and guinea pigs. Indeed, this would be a problem for years to come.[262] The Frenchmen, though, developed an ingenious alternative. Because of the close zoological relationship between sheep and goats, the French researchers undertook inoculation experiments from sheep to goats. They were successful and noted that the resulting disease in goats was slightly different than in sheep. Additionally, the dormant period was eight to nine months longer. Moreover, although the typical paralysis was similar, there was less of the cutaneous symptomatology manifested by significantly less itching and scratching in the goats. Thus, there seemed to be some evolution of the agent

[261] P. Lépine, "Sur le Virus Écossais de la Tremblante du Mouton (Louping Ill): Inoculation in Sheep," *Comptes Rendus des Séances de la Societé de Biologie et des se Filiales* 108 (1931): 399. My translation.
[262] Successful inoculation into laboratory mice would be done in 1961 by R.L. Chandler, "Encephalopathy in Mice Produced by Inoculation with Scrapie Brain Material," *The Lancet* 1, issue 7191 (June 24, 1961): 1378-1379.

in its passage from one species to another.[263] This would ultimately become a characteristic of the agents transmitting spongiform encephalopathies. Disease was slightly different when successfully transmitted across a species barrier, suggesting the transfer of genetic material able to code for the different proteins and enzymes that created these variations.[264]

John Russell Greig, like Gaiger before him, served as director of the Moredun Institute in Scotland and was also interested in scrapie. He noted in his 1940 article that he had "observed several instances which suggested the possibility that the disease could be transmitted through the medium of a pasture."[265] Recall that McFadyean had doubted this, while Stockman thought it probable. Recall, too, that there had been considerable difficulty transmitting it experimentally in a laboratory with only very recent success by the French researchers after failures by German, French, and British scientists. So Greig arranged an experiment to test the hypothesis that pastures could somehow harbor the responsible organism derived from infected sheep and transmit it to healthy animals.

Beginning in November 1932, Greig confined infected sheep to an enclosed pasture. Carefully preventing any contact between the healthy and the diseased animals, he allowed healthy sheep to graze in the pasture after the infected animals had been removed. Over the course of four years, a significant number of the healthy animals

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[263] J. Cuillé and P.-L. Chelle, "Transmission Expérimentale de la Tremblante à la Chèvre" *Comptes Rendus de L'Academie des Sciences*, 208 (1939): 1058-1060.
[264] As if to underscore their own understanding of the importance of the work they had done, within the context of an international dialog as well as its primacy, Cuillé and Chelle published a brief, but excellent, summary of their research in an English translation, making it available to a wider audience: Jean Cuillé and Paul-Louis Chelle, "Investigations of Scrapie in Sheep," *Veterinary Medicine* 34, no. 7 (July 1939): 417-418.
[265] J. Russell Greig, "Scrapie: Observations on the Transmission of the Disease by Mediate Contact," *The British Veterinary Journal* 96 (1940): 203.

contracted the disease, "indicating that scrapie is an infective disease, that the incubation period is prolonged, and that the causal agent can be transmitted through the medium of pasture."[266] His pathological examination also revealed, "the presence of vacuolation in the nerve cells, and vacuoles typical of those now regularly found present in scrapie were observed."[267] Others, including McFadyean and Gaiger, had denied finding anything of consequence in the brains of infected sheep. Greig's assertion that vacuolization of the brain cells was typical, expected, and commonly found reveals, another example supporting Kuhn's assertion that scientists begin to 'see' things within the framework of a newly accepted paradigm that had gone unnoticed before.

Work on other diseases due to filterable viruses was also carried out during this period, and one of these, as noted above, was louping ill, an encephalomyelitis caused by a tick-borne virus. By 1935, a vaccine had been developed to prevent louping ill in sheep and was put into a trial, which showed it to be quite effective, reducing disease from 9% to 1% among the vaccinated animals.[268] However, the trial also led to a coincidental, and unintended, experiment confirming the transmissibility of scrapie, which Cuillé and Chelle were also in the process of demonstrating with their research in France and which Greig was also investigating with respect to pastures.

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[266] Greig, "Scrapie: Observations on the Transmission of the Disease by Mediate Contact," 204.
[267] Greig, "Scrapie: Observations on the Transmission of the Disease by Mediate Contact," 205.
[268] W.S. Gordon, "Advances in Veterinary Research: Louping-ill, Tick-borne Fever, and Scrapie," *The Veterinary Record* 58, no. 47 (November 1946): 517. See also, J. Russell Greig, "Scrapie in Sheep," *The Journal of Comparative Pathology* [successor to *The Journal of Comparative Pathology and Therapeutics*] 60 (1950): 263-266.

By chance, one or more of the sheep whose tissues had been used to produce the louping ill vaccine had unrecognized scrapie prior to being sacrificed, and these tissues had been included in 'Batch No. 2' of the vaccine. Because of the possibility of live viruses remaining in these tissues and solutions, the preparation of the vaccine had included exposure to a formalin solution designed to kill the intended, louping-ill virus but also any unintended, stray viruses possibly contaminating the vaccine. The formalin certainly inactivated (killed) the louping-ill virus; however, many sheep vaccinated with Batch No. 2 began developing scrapie two years, or more, after inoculation. From this inadvertent 'experiment,' Greig and Gordon inferred that the agent of scrapie was present in the central nervous system (brain and spinal cord) and/or spleen of healthy sheep harboring a subclinical infection. Moreover, healthy animals could be infected through subcutaneous inoculation, with an incubation period of about two years. Most importantly, and somewhat ominously though, whatever the actual agent was, it was not killed by the usual method use to kill viruses: exposure to formalin.

Thus, by 1940, the transmissible agent responsible for scrapie was conceptualized as a filterable virus that was microscopically invisible. Or, in the scientific parlance of the period, it was ultramicroscopic of a size less than the wavelength of visible light. It almost certainly included some genetic component able to account for the symptomatic variations seen in sheep and the slight variation observed when transmitted from sheep to goats. Importantly and unexpectedly, it was resistant to formalin and "apart from the incubation period proper, the infective agent can remain latent but potentially infective in

the tissues of the living animal for an indefinite period during which it is capable of being activated so that it produces manifest disease."[269]

Over the next decade, other British scientists would show that there were at least two different strains of scrapie. When transmitted to goats, the causative agent of scrapie produced either a variation of the disease characterized primarily by drowsiness or primarily by scratching. Moreover, when recovered from these infected goats, the agent then bred true. That is, transmission from drowsy goats produced the same drowsy symptoms and the agent transmitted from scratchy goats produced the same scratchy symptoms. Because differences in various microbial strains are the result of different genes, it seemed obvious that these different strains of the agent reflected a difference of genetic make up. This naturally implied the presence of nucleic acids, the molecular carriers of genetic differences. Furthermore, the work of Richard Chandler in the early 1960s in transmitting scrapie to mice was only successful with the drowsy strain, further validating the importance of the different genetic strains of the agent.[270]

Iceland

In Iceland, the name for scrapie is *rida*, an Icelandic word for trembling. Rida (scrapie) had been present since the late nineteenth century but limited to the very northern part of the island.[271] Coincidentally, a small flock of sheep was imported into Iceland from Germany in 1933, bringing in several new diseases and spurring the

[269] Greig, "Scrapie in Sheep," 265.
[270] Schwartz, *How the Cows Turned Mad*, 45-50.
[271] Sigurdur Sigurdarson, "Epidemiology of Scrapie in Iceland and Experience with Control Measures," *Sub-acute Spongiform Encephalopathies: Proceedings of a Seminar in the CEC Agricultural Research Program*, Held in Brussels, 12-14 November 1990 (Boston: Kluwer Academic Publishers, 1991), 233-242.

foundation of the Keldur Institute for Experimental Pathology at the University of Iceland under its first director, Björn Sigurdsson.[272] One of these new diseases was maedi, a chronic pneumonia of sheep that seemed to incubate for a period of two to three years and always proved fatal. Visna, an inflammation of the brain and spinal cord in sheep was the other disease brought in with maedi. None of the sheep imported in 1933 actually developed the diseases, and it was not until about six years later that Icelandic sheep began to show signs of maedi.[273] Ultimately, Sigurdsson's work led to the understanding of maedi and visna as different manifestations of infection with the same virus, now known as Maedi-Visna virus (MVV).[274] Based on his experience with MVV, Sigurdsson began to develop a new concept of 'slow virus' infections. In fact, due to this work, viruses such as MVV are now referred to as lentiviruses.[275]

Maedi and rida obviously did not follow the kind of acute course characteristic of measles, polio, influenza, or other acute diseases, which entered a host, multiplied quickly and either overcame the host's defenses, or were overcome by the host's immune system in a few days or weeks. On the other hand, though, maedi and rida were not like the usual chronic infections such as the spirochete of syphilis or varicella (chickenpox) virus, which may linger, dormant in the body after an acute course only to reemerge years later, resulting in tertiary syphilis or shingles. In such a case, argued Sigurdsson, "the immunity mechanism of the body never gets a good grip on the pathogenic microbe and

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[272] Björn Sigurdsson, "Maedi, A Chronic Progressive Infection of Sheep's Lungs," *The Journal of Infectious Diseases* 90, no. 3 (May-June, 1952): 233-244.
[273] Sigurdsson, "Maedi, A Chronic Progressive Infection of Sheep's Lungs," 233.
[274] Otto Christian Straub, "Maedi-Visna Virus Infection in Sheep: History and Present Knowledge," *Comparative Immunology, Microbiology, and Infectious Diseases* 27, no. 1 (January, 2004): 1-5.
[275] The best-known lentivirus, of course, is the human immunodeficiency virus (HIV).

therefore a long and dubious battle ensues."[276] In the case of rida and maedi, however, Sigurdsson believed there was a significant difference from the usual chronic course. Instead of dormancy, he postulated a very long, slowly evolving subclinical course of disease that did not produce any symptoms or signs indicating its presence, but the viral agent was, nonetheless, still active. He even suggested that there was little, or no, immune response to what he had begun to call 'slow viral infections' and in which he had begun to include rida (scrapie). It is a moot point whether one considers this a new paradigm or an expansion of the existing viral paradigm. In either event it was new knowledge.

For example, his examination of the cerebrospinal fluid (CSF) in cases of rida revealed the presence of a previously unsuspected "silent meningitis" that was not apparent on clinical examination. It occurred "soon after the original infection [but] many months before clinical signs of encephalitis [were] noticeable."[277] Even so, the numbers of white blood cells found in the CSF of rida-infected sheep did not amount to the usually impressive response seen for meningitis; at most, it was a very modest immune response. For Sigurdsson, the hallmarks of 'slow viral infections' included a long latency interval of months or years, restriction of the infectious agent to a single host and usually to a specific organ system, and a regular, if protracted, course of fatal illness. The key was that it was not inactive; it was just very long and protracted in its evolution within the host.

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[276] Björn Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," *British Veterinary Journal* 110, no. 9 (September 1954): 350. Sigurdsson also noted on page 344 of this article that rida "occurs only sporadically" in certain areas.

[277] Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," 351.

In a 1952 article, he spoke about "a very long incubation period" for maedi.[278] However, in a 1954 article about maedi, he had begun to distinguish between a period of incubation and one of latency. It was not that the virus was inactive; rather, its activity was very subtle and its effects were not yet visible,

> It seemed possible that the incredibly long incubation period was really not a period of inactivity at all but that extremely slowly progressing anatomical lesions were developing, perhaps all the time from the moment of effective exposure until clinical signs became noticeable.[279]

Because he equated chronic diseases with diseases having irregular, protracted and unpredictable courses, Sigurdsson also disapproved of the use of the term 'chronic' when discussing the course of either maedi or rida. These, he argued, followed long but predictable courses.

Sigurdsson's concept of, what he called, "slow virus infections" was crucial to later scientists.[280] Carleton Gajdusek, for example, credited the Icelandic scientist with creating a new conceptualization of viral infection that ultimately allowed Gajdusek and others to look beyond the paradigm he "had learned to expect in acute, self-limited viral infections."[281] This was crucial when the similarities between scrapie and kuru finally were pointed out; the similarities were easier to understand, easier even to see, with the new concept of the slow virus available to provide a conceptual framework. Sigurdsson

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[278] Sigurdsson, "Maedi, A Chronic Progressive Infection of Sheep's Lungs," 233.
[279] Björn Sigurdsson, "MAEDI, A Slowly Progressive Pneumonia of Sheep: An Epizoological and Pathological Study," *The British Veterinary Journal* 110 (1954): 264.
[280] Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," 352.
[281] Gajdusek shared the Nobel Prize for work done on slow viral infections. See, D. Carleton Gajdusek, "Kuru in New Guinea and the Origin of the NINDB Study of Slow, Latent, and Temperate Virus Infections of the Nervous System of Man," in *Slow, Latent, and Temperate Virus Infections* ed. D. Carleton Gajdusek, Clarence J. Gibbs, Jr. and Michael Alpers (Washington, US Public Health Service – NIH, 1965): 3-12, 5.

had expanded the horizons of the paradigm making it easier (Kuhn would probably say 'making it possible') for researchers to see empirical evidence in the light of new interpretive choices and correlate animal TSEs with similar diseases in humans.

Because he died prematurely in 1959 at the age of forty-six, it is likely that Sigurdsson had not completely worked out his final conceptualization of slow viral infections.[282] He did, however, suggest that the paradigm of acute infections could be deceptive and misleading. That is, investigators approaching any new infectious process with the theories developed from the older, well-known paradigm of acute infectious processes could easily be misled and possibly misinterpret data, because they would predictably try to make the new infection fit into the older, more familiar paradigm.[283]

He also pointed out the importance of some unknown environmental factor in the transmission of rida, because something in the environment of the pasture sheltered the pathogenic agent. Moreover, the neuropathological findings in rida sheep were not particularly unusual, just subtle: they "were of the ordinary inflammatory type … of the type generally found in encephalitis of virus origin."[284] He noted that the inflammatory cells were usually "scattered foci of microglia."[285] Moreover, further experiments and

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[282] A decade later, Carleton Gajdusek would enunciate *his* understanding of Sigurdsson's definition of a slow virus infection as, "a progressive pathological process caused by an agent that remained clinically silent for along incubation period of months to years, and then produced disease with chronic accumulating disability." See, Gajdusek, "Kuru in New Guinea and the Origin of the NINDB Study of Slow, Latent, and Temperate Virus Infections of the Nervous System of Man," 5.
[283] Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," 353.
[284] Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," 343.
[285] Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," 343. This

autopsies performed before the development of clinical signs revealed that out of eleven sheep developing an immediate inflammatory response after inoculation, only four actually developed the clinical signs of rida, "suggesting that even after intracerebral inoculation rida often develops as a silent infection only, and we can speculate that such silent, unrecognized cases may play a role in the epizootiology of the disease."[286]

By the middle of the twentieth century, then, scrapie had become conceptualized as an infectious disease characterized by a long a latent period. It was not consistently or virulently contagious, but could be transmitted among sheep and across the species barrier to goats. It could also be spread by some environmental factor involved in pastures or fields. Importantly, the infectious agent seemed to be a virus: ultramicroscopic and filterable. The latency period was subclinical and made the disease essentially invisible, but it was nevertheless, still transmissible and became an important aspect of the new concept of infectious diseases: a slow viral disease whose viral agent apparently contained nucleic acids and was not inactivated by formaldehyde. Nor did the putative virus seem to evoke the sort of inflammatory reaction scientists commonly associated with viral infections, especially those involving the central nervous system. Sigurdsson's work seemed to suggest that, at best, any inflammatory reaction was modest and so early in the course of infection that it might be entirely missed when the disease progressed to the more obvious, clinical stage.

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rather technical aspect of the disease is included because later scientists assessing the changes in the brain have often denied the presence of any inflammatory response, even while other scientists claim to see a microglial inflammatory response. This, of course, recalls Kuhn's contention that scientists working within different paradigms 'see' different things and sometimes do not see what others do see.

[286] Sigurdsson, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics," 346.

Chapter 4

Kuru, the Slow Virus in Human Disease, and The Nobel Prize, 1958-1976

On the other side of the world, far away from Europe and Iceland, a new human disease had been discovered during the 1950s in the New Guinea highlands. It was called kuru by the indigenous tribes of the Fore region. The Fore people of New Guinea were essentially unknown to the outside world, and vice versa, of course, until the 1930s when airplanes first flew over the area, frightening, and leaving a lasting impression on, these isolated inhabitants still living in stone-age conditions.[287] The highland region of the Fore consists of rough, mountainous terrain above 5,000 feet. Not unexpectedly, the first explorers were miners in search of gold to mine; they were quickly followed by missionaries in search of souls to save. Then came the anthropologists, eager to document the newly discovered stone-age cultures, and among the first were Ronald and Catherine Berndt who did their field work in the early 1950s.

In addition to tribal wars, many of these isolated communities, including the Fore, engaged in ritualistic mortuary cannibalism. Beginning with the end of the Second World War, the governing authorities in Australia gradually suppressed this ritualistic consumption of deceased relatives, just as they suppressed intertribal hostilities and the endemic warfare among the tribes and villages. The Berndts were particularly interested

[287] Catherine H. Berndt, "Socio-Cultural Change in the Eastern Central Highlands of New Guinea," *Southwestern Journal of Anthropology*, vol. 9, no. 1 (Spring, 1953): 116-117.

in the ways in which the Fore culture adapted to the changes being forced on them. The couple described these changes dictated by the Australian overseers as a transition from "internal to external control" and they believed it to be "linked with the most striking and drastic alteration in the local social structure."[288] The Fore tribe members were among the last groups to be pacified in the area. They were still resisting the government injunctions against intertribal warfare as well as cannibalism, and they were still consuming their dead family members in ritual feasts well into the 1950s.

The bodies of those dying of contagious diseases were not consumed; instead, those bodies were buried to prevent infection of the living. In fact, the Fore had originally been reluctant to consume kuru victims for fear that it was contagious, but after conceptualizing the disease as the result of sorcery, they began consuming its victims too.[289] These mortuary feasts persisted longest in the South Fore region, which also had the highest incidence of kuru. Women and children of both sexes did most of the work preparing and cooking the remains. They were also more prevalent at the feasts, during which the entire body was consumed including the brain. For various reasons, the men of

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[288] C. Berndt, "Socio-Cultural Change in the Eastern Central Highlands of New Guinea," 120.

[289] In addition to ritual significance, the Fore found the taste of human flesh to their liking; to them, it was savory. The Fore of the more northern region also consumed the bodies of enemies in a version of 'vengeance cannibalism,' but the South Fore people did not. In the south it was solely linked to kinship rituals. See Robert Glasse, "Cannibalism in the Kuru Region of New Guinea," *Transactions of the New York Academy of Sciences* (April 1967), vol. 29, no. 6: 748-754, 750-1. Though this was presented to the New York Academy in 1967, the manuscript was written in 1962 based on their fieldwork carried out from 1961-1962. See, Robert Glasse and Shirley Lindenbaum, "Fieldwork in the South Fore: the process of ethnographic inquiry," in *Prion Diseases of Humans and Animals*, eds. Stanley Prusiner, John Collinge, John Powell, and Brian Anderson (Chichester: Ellis Harwood, 1992), 77-91, 85.

the South Fore culture tended to shun the practice and did not participate to the same extent as the women and children.[290]

A government patrol officer was the first, non-native outsider to report the affliction called kuru on December 6, 1953. The Fore verb *kuru* means to shiver or shake, and the disease is characterized by involuntary shivering and trembling.[291] The officer noted in his letter that the Fore believed kuru was caused by sorcery:

> I observed a small girl sitting down beside a fire. She was shivering violently, and her head was jerking spasmodically from side to side. I was told she was a victim of sorcery, and would continue this shivering unable to eat until death claimed her within a few weeks.[292]

Sorcery was not an unusual cultural practice among the various inhabitants of New Guinea, and Ronald Berndt based his anthropological understanding of sorcery on Bronisław Malinowski's earlier work, adopting the latter's belief that one function of sorcery was "enforcing conformity to certain rules or norms."[293] Interestingly, Catherine Berndt also noted that Seventh Day Adventist missionaries tried to enforce their cultural norms on the Fore "warning, for instance, that sickness will come to those who disobey them."[294] The Berndts were interested in kuru and they naturally approached this unusual new disease from their backgrounds as anthropologists.

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[290] Glasse and Lindenbaum, "Fieldwork in the South Fore: the process of ethnographic inquiry," 87-89.
[291] Recall that one name for scrapie in French was *la Tremblante*.
[292] Quoted in, V. Zigas and D.C. Gajdusek, "Kuru: Clinical Study of a New Syndrome Resembling Paralysis Agitans in Natives of the Eastern Highlands of Australian New Guinea," *Medical Journal of Australia*, vol. 11, no. 21 (November 23, 1957): 746.
[293] Ronald Berndt, "A 'Devastating Disease Syndrome:' Kuru Sorcery in the Eastern Central Highlands of New Guinea," *Sociologus*, vol. 8 (1959): 7.
[294] C. Berndt, "Socio-Cultural Change in the Eastern Central Highlands of New Guinea," 122.

The purpose of sorcery, Ronald wrote, is "to bring about physical pain, illness, injury, or death [or] to cause some mental or emotional disturbance in the victim; and kuru comes under this heading."[295] His discussions with members of the Fore predisposed him to think of it as a reaction to perceived sorcery, because such was the Fore people's own conceptualization of the disorder. Catherine agreed and also alluded to fatal outcomes among women afflicted by sorcery.[296] Working within the intellectual framework of a social science and trained to search for causation among societal relationships, they understood kuru to be the psychological manifestation of social beliefs severe enough to even cause death among its victims. Not surprisingly, they failed to consider the unlikely possibility of a completely unknown disease and, instead, explained it in terms of something they understood and knew well: sorcery. Importantly, though, their interpretation fit with the known facts and their anthropological methods; furthermore, the concept of an unknown disease was likely beyond their grasp, as it would be for many investigators to follow. Or, as Kyle Stanford would put it, "even the ability to engage in detailed and systematic observation and detection … of the objects of our theorizing seems to offer no proof against the relevance or centrality of the problem of unconceived alternatives."[297]

In 1955, Vin Zigas was the first medical officer to evaluate a kuru patient, and he was to be crucial in enlisting and aiding Carlton Gajdusek with the latter's efforts to understand the disease. Zigas reported to the Australian authorities in late 1956, outlining

[295] R. Berndt, "A 'Devastating Disease Syndrome:' Kuru Sorcery," 6.
[296] C. Berndt, "Socio-Cultural Change in the Eastern Central Highlands of New Guinea," 115.
[297] Stanford, *Exceeding Our Grasp*, 130.

his suspicions that the malady was "probably a new form of encephalitis.'"[298] His letter set in motion an epistolary conversation about the disease among Australian researchers, one of whom noted in early 1957 that Gajdusek had already "gone to the highlands."[299] Indeed, Gajdusek had visited New Guinea the year before and had become so fascinated with the people and the culture that he planned a sojourn there as part of his return trip back to the United States.

By all accounts Daniel Carlton Gajdusek was extraordinarily intelligent. MacFarlane Burnet, a renowned Australian virologist who won numerous awards including a Nobel Prize and a knighthood for his own exceptional work, reckoned Gajdusek was a true genius. Burnet's invitation to work with him in Australia was the reason Gajdusek was in the South Pacific when kuru was first observed. However, after working with him for a year, Burnet evaluated Gajdusek thus:

> … he has an intelligence quotient up in the 180s and the emotional immaturity of a 15-year-old. He is quite manically energetic when his enthusiasm is roused, and can inspire enthusiasm in his technical assistants. He is completely self-centered, thick-skinned, and inconsiderate, but equally won't let danger, physical difficulty, or other people's feelings interfere in the least with what he wants to do. He apparently has no interest in women, but an almost obsessional interest in children, none whatsoever in clothes or cleanliness: and he can live cheerfully in a slum or a grass hut.[300]

Gajdusek was also quite frenetic, and it was not unusual for him to lecture with two slide projectors working simultaneously while he narrated a streaming video on a

[298] Zigas to Gunther, 26 December 1956, in *Kuru: Early Letters and Field-Notes from the Collection of D. Carlton Gajdusek,* eds. Judith Farquhar and D. Carlton Gajdusek (New York: Raven Press, 1981), 1.
[299] Gunther to Burnet, late February 1957, in *Kuru: Early Letters and Field-Notes* 3.
[300] Burnet to Gunther, mid-April 1957, in *Kuru: Early Letters and Field-Notes* 41.

third screen.[301] And, as if to prove the veracity of Burnet's last observation (written in April 1957), Gajdusek documented a night spent in a grass hut on a remote trail in New Guinea. He recounted the hardship of the trail itself, but that night, bivouacking in the jungle alongside the trail, he was perfectly content listening to a Beethoven concerto on a portable radio, enjoying a bottle of red Bordeaux, and reading George Orwell's *1984*. He wrote in his ever-present journal that one "could not possibly hope for greater luxury (all this with a night of guard watch-fires burning, posted in the event of [hostile] attack, in a region only twice previously visited by Caucasians)."[302]

As a child, Gajdusek had been an avid reader of scientific biographies, especially those dealing with the great men of nineteenth century science who discovered and characterized so many infectious organisms. His aunt arranged for him to do precocious work in a laboratory even before college where he matriculated at the young age of 16. Even as a teen-ager his scientific work was exemplary and precocious. Allowed to follow research work involving the development of a new chemical weed killer, he had documented the scientists' work so meticulously with such complete and well written notes that the Boyce Thompson Institute for Plant Research was later able to use them (instead of their own scientific notes) to obtain a patent for the chemical process developed while he observed there as a sixteen-year-old boy.[303]

Preternaturally gifted, Gajdusek graduated *summa cum laude* from the University of Rochester before his twentieth birthday and headed to Harvard for medical school in

[301] Raymond Roos, "D. Carlton Gajdusek," *Proceedings of the American Philosophical Society*, vol. 159, no. 1 (March 2015): 101-4.
[302] Carleton Gajdusek, "Excerpts from Field-Journals: Kuru Epidemiological Patrols, 26 September – 9 November 1957," in *Kuru: Early Letters and Field-Notes*, 197.
[303] Anderson, *The Collectors of Lost Souls*, 35.

1943. He had no interest in clinical medicine, and after a pediatric residency, he gravitated towards research and found himself working and hobnobbing with many of the great scientific minds of the post war period: Linus Pauling, Max Delbrück, James Watson, and Wendell Stanley.[304] Indeed, his early career after medical school was remarkable for the number of Nobel Prize winners with whom he worked; others included John Enders and Burnet. In the end he created a career out of his peripatetic lifestyle spent searching for pathogenic microbes in far-flung locales such as the remote Hindu Kush of Afghanistan, Iran, Turkey, and the jungles of South America.[305] It was, of course in the rain forests of New Guinea that he would find kuru.

The middle decades of the century were the heyday of viruses in general and, perhaps, the oncovirus (viruses that caused tumors and cancers) in particular. The electron microscope was invented during the 1930s, though it was not initially expected to be helpful to biologists. On the contrary, it was assumed that a beam of high-energy electrons would simply incinerate, rather than image, biological specimens. Fortunately, this fear was unjustified and German research physician, Helmut Ruska, and his brother, Ernst, published the first images of a virus in 1940. The latter received the 1986 Nobel Prize for his work developing the electron microscope; Helmut died before the prize was awarded.[306] The images were, of course, tobacco mosaic virus, the ubiquitous workhorse of early virology. After the war, images of viruses began to multiply and investigators finally had the kind of empirical access to viruses that they had enjoyed with bacteria for well over a hundred years, even though Jules Bordet (winner of the 1919 Nobel Prize for

[304] Anderson, *The Collectors of Lost Souls*, 35-38.
[305] Roos, "D. Carlton Gajdusek," 98.
[306] D.H. Kruger, *et al*., "Helmut Ruska and the Visualization of Viruses," *The Lancet* 355 (May 13, 2000): 1713-1717, 1713.

Physiology or Medicine) decried its usefulness: "it's troublesome enough to interpret the images we get by the light microscope."[307] His fears were unfounded and images of viruses proved revelatory, allowing scientists to distinguish not only the ultramicroscopic structure of viruses but also to distinguish among different viruses.

One of these scientists was Aaron Klug. Though German born, Klug grew up in South Africa; received his doctorate from Cambridge University; and worked with Rosalind Franklin before her untimely death in 1958. Klug was knighted, elected to the Royal Society, and awarded the 1982 Nobel Prize in chemistry for using of X-ray diffraction techniques combined with electron microscopy to decipher the size and shape of viruses along with their methods of self-assembly.[308] Thus, the structure of viruses began to take shape: a core of nucleic acid surrounded by a protective jacket of protein. In 1978, Klug defined the virus for a scientifically literate public:

> Viruses are complex particles made up of inert giant molecules: proteins and nucleic acids (DNA or RNA). They are dead in the sense that they lack any internal metabolism, but they come alive on entering the living cell. For this reason they are obligate parasites, able to reproduce only by taking over the enzymatic machinery of the host cell.[309]

Now, viruses could be seen, imaged, characterized, and distinguished from bacteria and other microbial organisms. They were no longer defined by what they were not: unseen, unfiltered, and uncultured.

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[307] L. Marton, *Early History of the Electron Microscope* (San Francisco: San Francisco Press, 1968), v-vi and 24. Grafe, *A History of Experimental Virology*, 98-99. Collard, *The Development of Microbiology*, 166.
[308] Linda A. Amos and John T. Finch, "Aaron Klug and the Revolution in Biomolecular Structure Determination," *Trends in Cell Biology* 14, no. 3 (March 2004): 148-152, 148.
[309] P. Jonathon G. Butler and Aaron Klug, "The Assembly of a Virus," *Scientific American* 239, no. 5 (November 1978): 62-69, 62.

In his 1940 first edition of *Natural History of Infectious Disease*, MacFarlane Burnet could list only 25 viral diseases of humans. This number increased dramatically during the ensuing decades. In the 1962 edition, Burnet noted that it was no longer possible to give a precise number, but "there are probably about a hundred different viruses capable both of causing a significant human illness and of being identified in a fully equipped virus laboratory."[310] Burnet was especially interested in the evolutionary interactions of viruses with humans in their natural environment, and this intrigued Gajdusek too. It is clear that Gajdusek was becoming a staunch advocate of the importance of viruses in human diseases and was beginning to think like a virologist.[311] His thinking was almost certainly predisposed to a viral etiology in the case of a new or poorly understood disease, and kuru was both new and poorly understood when Gajdusek arrived in New Guinea early 1957.

It is important to note, however, that prior to about 1965, medical virologists dealing with viral diseases of humans dealt with the more common viral diseases such as measles, smallpox, and poliomyelitis that were quickly and virulently manifest after a very short incubation period. Moreover, the usual viral infection was seemingly always accompanied by an appropriate and stereotypical (though not necessarily successful) immune response within a host animal. This was the commonly accepted nature of viral disease in the relatively early days of modern virology when Gajdusek was actively studying kuru in New Guinea.[312] This was the bias he carried with him when he began

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[310] Sir MacFarlane Burnet, *Natural History of Infectious Disease*, 3rd edition (Cambridge: Cambridge University Press, 1962), 82-3.
[311] Anderson, *The Collectors of Lost Souls*, 47.
[312] I use the term 'modern virology' here quite loosely, suggesting that the visualization of viruses with the electron microscope ushered in a more modern understanding of them.

his investigation of kuru. It was only later, during and after the 1950s that virologists began to recognize the long periods of inactivity in certain human viral infections, such as herpes, varicella-zoster, human papilloma virus and others.[313]

Complicating the understanding of viral disease even more, Gajdusek would, much later, publish an article in 1967 that demonstrated the existence of dozens of apparently asymptomatic and coincidental viruses in the brains of monkeys experimentally infected with kuru. The authors even opined, "the internal milieu of an animal cannot be regarded as microbiologically sterile even in the case of such organs as the brain and spinal cord."[314] But this was in the future, and in 1957, Gajdusek's knowledge and scientific background were more heavily biased toward the traditional paradigm of acute viral disease with its obvious inflammatory response. Even so, while Gajdusek's work did not actually begin the understanding of chronic viral infections in humans, it certainly accelerated and expanded it.

Gajdusek soon learned that no outsider entering the Fore territory had ever contracted the disease and that 100% of the recently studied cases had proved fatal. Very few, if any, infectious diseases (or other diseases for that matter) are uniformly fatal. Even so, at that time, the leading etiologic explanation was a viral encephalopathy; recall that this had been the first impression of Vin Zigas. Other considerations included an

[313] Richard T. Johnson and Kenneth P. Johnson, "Slow and Chronic Virus Infections of the Nervous System," in *Recent Advances in Neurology*, ed. Fred Plum (Philadelphia: F.A. Davis Company, 1969), 33-78: 49-50.
[314] Nancy G. Rogers, M. Basnight, C.J. Gibbs and D.C. Gajdusek, "Latent Viruses in Chimpanzees with Experimental Kuru," *Nature* (November 04, 1967), vol. 216, no. 5114: 446-449, 449.

unknown toxin or a possible deficiency of, for example, copper or manganese.[315] Because kuru victims included young children, Gajdusek's nimble mind had already eliminated such etiologies as familial neuropathies, degenerative diseases, and atherosclerotic diseases, which mainly occur in adults. There was also a pronounced predilection for females as well as children. Years later, Gajdusek summarized the clinical course of the disease: invariably fatal, it begins with difficulty walking, coordinating movements of the limbs, trembling, shivering, emotional lability, incongruous and compulsive laughter and eventually proceeds to complete debilitation with loss of ability to ambulate or even sit upright. There was no evidence of the sort of symptoms or signs characteristic of known infections such as "Fever, sore throat, sore eyes, coughs, mucous discharges or rash."[316] Realizing the importance of a more complete clinical evaluation than he could perform in the bush, Gajdusek initiated efforts to transfer a patient to a specialized hospital in Australia for evaluation and probable autopsy.

Although Gajdusek was quick to assert that he was "not suggesting accepting a classical early case in Melbourne on the Clinical Unit for autopsy purposes," he was probably being disingenuous. He had, in fact, already noted the 100% mortality rate of kuru.[317] Consequently, lacking some miraculous, and immediate, insight into the disease by Australian specialists, he must have been confident the outcome in Melbourne would,

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[315] Scragg to Anderson, 5 March 1957, in *Kuru: Early Letters and Field-Notes* 3-4.
[316] P.P. Liberski and D.C. Gajdusek, "Kuru: Forty Years Later, A Historical Note," *Brain Pathology* (January 1997), vol. 7, no. 1: 555-560, 557.
[317] DCG to Burnet, Wood, and Anderson, 13 March 1957, in *Kuru: Early Letters and Field-Notes* 5-6.

in fact, be fatal, and would most likely be followed by an autopsy.[318] Only a few days later, for example, he declared to the senior public health officer, "what is most urgently needed is expert neuropathology of an entire, well-fixed brain, with all types of staining techniques and long-term study."[319] He was correct on all counts. With no real understanding of the disease from the tests already done and no response to various obvious treatments, there was little likelihood that physicians in a larger hospital would prevail against the disease with their first cases. Moreover, in the end it would be the basic neuropathological findings that would trigger the realization that kuru is related to scrapie and begin to define the etiology of the disease.

Igor Klatzo in Washington, D.C. performed the initial neuropathological examination of brain specimens using materials supplied by Gajdusek. However, his analysis did not provide any definitive answers. Klatzo considered it a new disease, and he certainly did not find any indication it was inflammatory or infectious. Though he did mention a resemblance to Creutzfeldt-Jacob disease, he essentially dismissed any connection because of numerous clinical and pathological disparities. It did not resemble any of the known hereditary degenerative diseases, and he could only suggest the possibility of a new, unknown "toxic metabolism responsible for the process."[320]

[318] Most cases died locally and in the presence of their family members who refused autopsy requests. One cannot avoid hearing here a faint echo of the early Tuskegee investigators arguing for the importance of autopsies despite the wishes of patients and families.
[319] DCG to Scragg, mid-March 1957, in *Kuru: Early Letters and Field-Notes* 14-15.
[320] Klatzo to DCG, 13 September 1957, in *Kuru: Early Letters and Field-Notes* 155-156.

Importantly, though, Klatzo provided Gajdusek with photomicrographs of the damage done to the brain by the disease.[321]

The first in depth medical study of kuru was done by Gajdusek and Zigas together and published almost simultaneously as two similar articles, one in the *New England Journal of Medicine* and the other in *Medical Journal of Australia*. Though they had initially thought they were dealing with a viral encephalitis or post-encephalitic process, they could find none of the hallmarks of these established infectious processes. Consequently, they ruled this out in their initial articles: "[we] must reluctantly conclude that kuru is apparently not of post-infectious ætiology."[322] Seemingly, they also overlooked the importance of the Fore custom of cannibalism, mentioning only in passing that "even at present remnants of these practices survive."[323] Gajdusek was truly in his element: an exotic, tropical locale hot on the trail of a mysterious, new disease. If only it had been more obviously infectious, he could have written himself into his favorite boyhood fantasies derived from Paul de Kruif's *Microbe Hunters*. But even in one of his first letters, we find mentioning the cannibalism without recognizing its importance:

> I am in one of the most remote, recently opened regions of New Guinea (in the Eastern Highlands), in the center of tribal groups of cannibals only contacted in the last ten years and controlled for five years – still spearing each

[321] Igor Klatzo, D.C. Gajdusek, and V. Zigas, "Pathology of Kuru," *Laboratory Investigation* 8, issue 4 (1959): 799-847. This article has clear and revealing photomicrographs revealing vacuolization of neurons and brain tissues.
[322] Zigas and Gajdusek, "Kuru: Clinical Study of a New Syndrome Resembling Paralysis Agitans," *MJA*, 752.
[323] Zigas and Gajdusek, "Kuru: Clinical Study of a New Syndrome Resembling Paralysis Agitans," *MJA*, 746.

> other as of a few days ago, and only a few weeks ago cooking and feeding the children the body of a kuru case, the disease I am studying.[324]

Here in the letter was the crucial piece of the puzzle, apparently overlooked despite being in plain sight: the oral ingestion of diseased tissue. However, it is misleading to suggest it was simply overlooked, because there was good reason to discount its importance.

While ritualistic endocannibalism was not confined to the Fore, kuru *was* basically confined to the Fore. Although there were a few cases in surrounding tribes, these unfortunate individuals had, as will be discussed below, connected themselves with the Fore through intermarriage. Otherwise, kuru was essentially unknown in tribes remote from the Fore, even though they, like the Fore, consumed dead parents and family members. So, it was not unreasonable for Gajdusek to disregard cannibalism as the cause of the disease among the Fore. Indeed, to implicate it, he would have had to explain its absence among the other tribes, and this was beyond his imagination.[325] It would literally have required envisioning an almost inconceivable situation: the appearance of a sporadic case of Creutzfeldt-Jacob disease (which, at that time, was thought to be a degenerative disease and not known to be transmissible or even similar to kuru) among a tribe of endocannibals in the early twentieth century, which then became endemic through the ritual consumption of the first CJD victims and then became epidemic by consumption of

[324] DCG to Smadel, 15 March 1957, in *Kuru: Early Letters and Field-Notes* 8.
[325] Years later, Gajdusek would also ascribe his dismissal of cannibalism to finding "individuals whom we did not believe had engaged in the ritual cannibalistic consumption of diseased relatives." See, Gajdusek, "Kuru in New Guinea and the Origin of the NINDB Study of Slow, Latent, and Temperate Virus Infections of the Nervous System of Man," 3.

ensuing victims by the various surviving family members.[326] This is the best twenty-first-century explanation for the origin of kuru, and it fits the data that is known today. In the same way, earlier explanations such as a psychological reaction to sorcery or a genetic neurodegenerative disease also fit the data that were known during the period from the late 1950s to 1965. But, the present explanation was simply beyond the conceptual grasp of anyone at the time, because the crucial knowledge that kuru could, in fact, be transmitted from one person to another was completely unknown.[327]

After eliminating various possibilities such as toxic poisoning, even Gajdusek returned several times to the possibility of a psychosomatic disease, such as "fatal anorexia nervosa plus hysteria."[328] It is remarkable how often observers, both medical and non-medical, returned to this category of diseases. Without an essential piece of information (i.e. that the disease was transmissible), their minds always returned to the familiar, but there was no conventional category of infections that Gajdusek could use to conceptualize the disease. The notion of an infectious, transmissible, degenerative disease of the brain was totally unfamiliar. It was inconceivable and a concept beyond his intuition; to have correctly apprehended it at this stage would have been truly extraordinary and almost clairvoyant. After seeing numerous cases, he wrote, "all with the same neurological picture, afebrile and progressive; some four doctors beside myself have now seen it … all [are] impressed that it is a new epidemic syndrome of some sort

[326] Glasse, "Cannibalism in the Kuru Region of New Guinea," 750 and753. See also John D. Mathews, Robert Glasse, and Shirley Lindenbaum, "Kuru and Cannibalism," *The Lancet* (August 24, 1968), vol. 2, issue no. 7565: 449-452, 451.
[327] In one sense, kuru truly exemplifies Stanford's idea of inconceivable alternatives, because kuru is quite literally *sui generis.* It is unlikely that it ever appeared before or that ever will again.
[328] DCG to Burnet, Wood, and Anderson, 13 March 1957, in *Kuru: Early Letters and Field-Notes* 8.

of Parkinson or basal ganglia disorder (toxic, allergic, heredofamilial, post-infectious?? – or psychiatric?)."[329] The proper determination exceeded everyone's grasp.

In an interesting, and almost subconscious, allusion to the problem of unconceived alternatives, Gajdusek actually discussed the problem in a letter to his patron, Joseph Smadel, who was chief of the virology section of the National Institutes of Health in Bethesda, Maryland. Unable to find evidence of infection or inflammation, Gajdusek seemed to understand the need to entertain novel interpretations. He wrote, "I can still see no sign of infection or post-infectious phenomenon; but with something as unique and unprecedented as kuru, a unique and unprecedented explanation is required." Moreover, his mental musings were not far off target as he mulled over "some material which continues over many months to act after initial exposure." This last qualification was added to account for the few known cases of Fore tribe members developing kuru years after leaving the Fore region to join another tribe. As if to reassure himself that the elephant in the room, cannibalism, had nothing to do with the disease, he added, "Cannibalism as a possible source seems well ruled out."[330]

At this early stage, an extremely bizarre and unique complex of symptoms and signs defined the disease. These included insidious onset without evidence of an earlier febrile illness and no fever throughout the progression of the disease. Additionally, the clinical picture of the patients was distinctive:

> They were rational, but articulation of speech was very poor. Silly smiles, with grimacing, were prominent. Fixed and pained facies and slow, clumsy,

[329] DCG to Smadel, 15 March 1957, in *Kuru: Early Letters and Field-Notes* 9.
[330] DCG to Smadel, 16 November 1957, in *Kuru: Early Letters and Field-Notes* 253.

> voluntary motion (apparently in an attempt to overcome tremors and athetoid movement) were prominent also.[331]

Although Gajdusek had been skeptical of earlier descriptions, the reality impressed him greatly, and he realized that the Fore themselves could diagnose kuru as accurately as any modern physicians: "They know what they are talking about; and once you have seen a few cases, you also know."[332]

At this point, then, the disease was conceptualized clinically as a peculiar complex of singular motor abnormalities, as recognizable to the medically unsophisticated Fore as it was to western medicine. Understanding of the etiology of the disease, however, was something else. While the Fore considered it the result of sorcery, as the on site representative of modern western medicine, Carleton Gajdusek, was simply confused. He had been prepared to diagnose it as either viral encephalitis or as a post-viral encephalopathy, but he was forced to discard his theory-laden preconceptions, because the appropriate markers (fever and inflammatory cells in the cerebrospinal fluid) were not present. Unable to conceive of anything else, even he fell back on the possibility of some sort of psychosomatic illness, such as,

> … various types of hysteria and motor aspects of psychoses, such as behavior of certain schizophrenics – but the hysterical analogy is closer, for rationality is usually good early in the disease as well as late.[333]

This, of course, had been the diagnosis of Ronald Berndt, derived from his anthropological background.

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[331] DCG and Zigas to Burnet, Anderson, and Wood, 15 March 1957, in *Kuru: Early Letters and Field-Notes* 10.
[332] DCG and Zigas to Burnet, Anderson, and Wood, 15 March 1957, in *Kuru: Early Letters and Field-Notes* 10.
[333] DCG and Zigas to Burnet, Anderson, and Wood, 15 March 1957, in *Kuru: Early Letters and Field-Notes* 11.

However, it soon became apparent that though kuru was unknown in other parts of New Guinea and was primarily limited to members of the Fore linguistic community, there were a few cases among the nearby villages of other linguistic groups that had *intermarried* with their Fore neighbors. Moreover, the disease was clearly more manifest in certain families. Thus, after months of careful investigation, Gajdusek believed he could eliminate a post-infectious etiology, but he could not discount the possibility of genetic factors "probably in association with as yet undetected ethnic-environmental variables."[334]

This suggestion led to research looking for a hereditary etiology, and the findings were interesting. While the geneticists were certainly not dogmatic in their conclusions and emphatically stated that their hypothesis was only tentative, they did suggest that the available genealogical data supported at least a hypothesis of a genetic etiology.[335] Comparing genealogies developed by themselves and one generated by Gajdusek and Zigas, genetic researchers found good consistency and felt confident drawing conclusions. They determined that the evidence drawn from genealogies was consistent with kuru being a hereditary disease determined by a "single autosomal gene *K* dominant to its allomorph *k* in females and recessive in males."[336] The theory accordingly accounted for most of the oddities of the disease, such as the higher incidence in females, a distinct familial pattern, similarity to other degenerative neurological diseases believed

[334] D.C. Gajdusek and V. Zigas, "Degenerative Disease of the Central Nervous System in New Guinea," *New England Journal of Medicine* vol. 257 no. 20 (November 14, 1957): 977 and 978.
[335] J.H. Bennett, F.A. Rhodes, and H.N. Robson, "A Possible Genetic Basis for Kuru," *American Journal of Human Genetics*, vol. 11, no. 2 – part 1 (June 1959): 181.
[336] Bennett, et al, "A Possible Genetic Basis for Kuru," *AJHG*, 183. The trait being recessive in males would account for the much greater incidence of kuru among women.

to be hereditary, and occurrence at an earlier age in second generations.[337] In short, they wrote, "The genetic hypothesis which we have advanced for kuru provides a ready explanation for the family data which have been collected so far."[338]

This was a perfect example of the problem of underdetermination. The conceptualization of kuru as a genetic, hereditary disease fit nicely with the empirical data. In fact, however, kuru was almost certainly *not* transmitted genetically among the Fore. Rather, transmission was through oral ingestion of contaminated human tissue.[339] The specifics of the inheritance patterns are included here not to confuse the reader, but to show how successfully the geneticists had convinced themselves of the accuracy of their theory that kuru was indeed a genetic disease passing through specific, identifiable families. The situation highlights the problem of underdetermination: there are often multiple theories compatible with the same empirical evidence. As says Kyle Stanford says, history reveals that there have frequently been other alternative explanations, which were simply not imaginable to the investigator at the time.

On the other hand, however, it is now known that some of the human TSEs are transmitted to offspring through genetic inheritance, and it is not impossible that there was a genetic component to kuru. However, genetic transmission seems increasingly

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[337] For a good discussion of this fit between the evidence and the genetic theory, see Ann Fischer and J. L. Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru," *Journal of Health and Human Behavior* (Spring 1961), vol. 2, no. 1: 16-25, 18-21.

[338] Bennett, et al, "A Possible Genetic Basis for Kuru," *AJHG*, 185.

[339] Some authorities have suggested the possibility of an additional, or alternative, route: self-inoculation of contaminated tissue into the eyes or nasopharynx when preparing the tissues (especially the brain) of the deceased kuru victims in a situation of poor hygiene without adequate hand washing etc. This would certainly explain the high incidence of kuru among women and children: they were tasked with preparing the body of the dead, including the brain, for consumption.

unlikely for kuru since the disease has essentially disappeared with the disappearance of endocannibalism among the Fore. Even so, that could only have been ascertained in retrospect over the following decades, not during the early years of research.

Despite the fact that Gajdusek had discounted the role of cannibalism in the propagation of the disease, not all researchers were quite so dismissive. During the 1950s, for example, anthropologists had begun adopting the principles of biology and genetics to complement their more customary cultural explanations.[340] Another husband and wife team of anthropologists, Ann and John Fischer, reflected the usefulness of this biological anthropology when they presented well-argued evidence against the genetic etiology of kuru in a letter to *The Lancet* printed in the June 25, 1960 issue. They noted that women from kuru-free villages outside the Fore culture marrying into Fore villages and contracting kuru actually argued *against* a hereditary trait among the Fore. Likewise, their investigations suggested that the rate of genetic mutation necessary to sustain the disease "in the population is much greater than the known mutation rates for other pathological genes."[341]

Instead, the Fischers believed that the Fore culture presented an ideal situation for "an environmental agent to attack women and children and by-pass adult males, [and] that it would seem difficult to abandon the possibility of … a toxin, virus, or

[340] S. L. Washburn, "The New Anthropology," *Transactions of the New York Academy of Sciences* (May 1951), vol. 13, issue 7, series II: 298-304.
[341] Ann Fischer and John L. Fischer, "Æetiology of Kuru," *The Lancet* (June 25, 1960), vol. 275, issue no. 7139: 1417-1418, 1417. For a more complete explication of their evidence and reasoning, see Fischer and Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru," 18-21.

deficiency."[342] It is notable that in a 1961 article, but not in their 1960 letter to *The Lancet*, the Fischers cited the "recent article by Hadlow suggesting that kuru has certain resemblances to … *scrapie*."[343] So, Ann and John Fischer joined the international discussion about scrapie and added to the work to scientifically link it with kuru. Despite this very accurate reasoning, though, the Fischers primarily implicated the separate living conditions of men and women in Fore society for the preponderance of the disease among women. In fact, they noted the Fore male fear of menstruating females and astutely reasoned that a "virus which has any relevance to the menstrual cycle of women would be inevitably more effective against women, and, possibly, children than it would against men who have such strong taboos against contact with menstrual blood."[344]

Even so, second on the Fischers' list of possible correlations was the consumption of kuru victims, which "suggests a way in which a viral agent might be passed."[345] It was not their first consideration because they were not fully aware that Fore men usually declined to join in the funereal feasting; the earlier anthropologist, Ronald Berndt, had suggested that women may have been the main consumers but thought it would be difficult to prove.[346] This was a crucial bit of evidence implicating the cannibalization of kuru victims that was not available to them.

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[342] Ann Fischer and John L. Fischer, "Æetiology of Kuru," 1418.
[343] Fischer and Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru," 24. Italics present in the original.
[344] Fischer and Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru," 24.
[345] Fischer and Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru," 24.
[346] Fischer and Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru," 24.

Yet another pair of anthropologists, Robert Glasse and Shirley (Glasse) Lindenbaum had also noted the correlation between the gendered demographics of kuru cases and the main consumers of kuru victims. Initially working to establish the historical appearance of kuru among the Fore, they delved deeply into all aspects of kuru and the ritual of funereal cannibalism. They seem to have been the first researchers to confirm the lack of adult male participation in the consumption of the dead and to correlate that with the paucity of adult male victims of kuru. Most victims were women and small children who were the ones most likely to have ingested the flesh, or brain, of the deceased. Robert Glasse remarked that while the women particularly enjoyed the taste of human flesh, the children "consumed any food given to them by their mothers," and the men were finicky eaters who "believed that cannibalism robbed a man of his vitality."[347] Additionally, he argued that the noticeable decline of kuru among children was easily explained by the cessation of cannibalism after about 1956. This decline was otherwise difficult to explain. As he later recalled, it was during the month of June 1962 when, inspired by an article in *Time Magazine* (May 18, 1962) about the transfer of memory through cannibalization among flatworms, he began to appreciate the very real connection between the demographics of the disease and those who ate the victims.[348]

Later in 1968, after Gajdusek had successfully transmitted kuru to primates and shown it to be a transmissible disease, Glasse and Lindenbaum joined with John

[347] Glasse, "Cannibalism in the Kuru Region of New Guinea," 751.
[348] See Glasse and Lindenbaum, "Fieldwork in the South Fore: the process of ethnographic inquiry," for a discussion of the nature and timing of their work, especially pages 77-86. Jay Ingram notes that the research about memory transfer discussed in the *Time* article was not well supported, but that is beside the point. Just the concept of cannibalization transferring something to the consumer was enough to lead them to consider and explain the *demographics*, not the pathology, of the disease.

Matthews (an Australian physician also working in the Fore region) to compose an excellent epidemiological analysis of the kuru victims. Their data strongly suggested that the very low incidence of apparent horizontal transmission to men (who did not consume kuru victims) argued against a theory of genetic susceptibility in this tightly knit community of close kinships. If a genetic susceptibility were more important than the virulence of the transmissible agent, one would expect to see much more horizontal transmission to men given the number of victims within the community.[349] Of course, this too was underdetermined, because an agent with extremely low potential for infectivity (except by oral ingestion) would also explain their data. Moreover, present-day knowledge of the TSEs does implicate a certain degree of genetic susceptibility.

At this point in the history of kuru, one could justifiably opine that the anthropologists and geneticists were making more progress in understanding the disease than were the biomedical scientists. Despite Gajdusek's intuitive belief that it was a type of encephalitis, he simply had no evidence to corroborate his diagnostic instinct. He almost certainly wanted it to be a new infectious disease and he undoubtedly wanted to be the one to solve the problem. Despite the fact that he had become a staunch advocate of the viral etiology of diseases, there was simply no evidence that this one was, in fact, caused by any infectious agent, viral or otherwise. And, this was the situation until a serendipitous meeting took place in London.

William J. Hadlow trained as a veterinary pathologist and was well known for his belief in the importance of careful, methodical observation with an experienced eye, probably because he had more experience and a better eye than most. His ability to find

[349] Mathews, Glasse, and Lindenbaum, "Kuru and Cannibalism," *The Lancet*, 451.

abnormalities in the brains of animals dying of unusual diseases resulted in his often being called in by other pathologists to help them with their work; he was a consultant to consultants. He normally worked at the Rocky Mountain Laboratories in Montana, part of the National Institutes of Health, but his expertise was such that he was assigned to spend several years in England studying scrapie from 1958 to 1961. Later, in 1965, Hadlow was chosen to go to the Union of Soviet Socialist Republics with a group of other specialists in order to examine the work of Russian scientists who were purported to have successfully transmitted Lou Gehrig's disease (also known as, motor neuron disease, or amyotrophic lateral sclerosis) from humans to primates. It was during his sojourn in England, though, that Hadlow became involved in the international scientific discourse around scrapie and kuru. Moreover, while his involvement was coincidental, his contribution was pivotal.[350]

As he later wrote, an American parasitologist and colleague from the Rocky Mountain Labs, William Jellison, was passing through England and visited the Hadlows in late June of 1959. Over dinner, Jellison casually mentioned an interesting exhibition about an unusual disease he had encountered at the Wellcome Institute in London. Curious, Hadlow went to London a few days later to see it. The exhibit, of course, focused on kuru. In fact, Gajdusek, himself, had arranged it, outlining the disease and his research so far. The display included not only clinical information but also copies of the photomicrographs, made by Igor Klatzo at NIH in 1957, of the pathological changes found in the brains of its victims. These photomicrographs were the key and immediately

[350] K. Pekoc, "Obituary: William J. Hadlow," *Veterinary Pathology* (August 2015), vol. 52, no. 5: 985. See also, Jacob A. Brody, William J. Hadlow, *et al*., "Soviet Search for Viruses That Cause Chronic Neurological Diseases in the U.S.S.R.," *Science* (March 03, 1965), vol. 147, no. 3662: 1114-1116.

caught Hadlow's experienced and well-trained eye. He was impressed by the similarity of the pathological findings in the brains of kuru victims to the changes caused in the ovine brain by scrapie. The key feature was the vacuolization of the neurons, first seen and remarked by Besnoit and Morel in 1898: "Although unusual in human neuropathology, in veterinary pathology such vacuolated neuronal cell bodies had long been identified almost solely with scrapie," wrote Hadlow.[351]

Years later, Hadlow was still impressed with the tenuousness of the "unlikely linkage" between the two diseases.[352] For him, "it was but the consequence of a chance observation."[353] On the other hand, perhaps it should not be surprising that no one else had noticed the similarities. Kuru was a very new, obscure, and enigmatic disease, and would likely have been almost completely unknown among veterinary scientists, or even among most medical scientists working on human diseases. Likewise, scrapie was relatively unknown outside of a small circle of veterinarians, shepherds, and sheep ranchers.

Within weeks, however, *The Lancet* published Hadlow's communication about the resemblance and the proposed connection between the human and the ovine

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[351] William J. Hadlow, "Kuru likened to scrapie: the story remembered," *The Philosophical Transactions of the Royal Society*, Series B, Biological Sciences (November 27, 2008), vol. 363, no. 1510: 3644.

[352] William J. Hadlow, "Neuropathology and the Scrapie-Kuru Connection," *Brain Pathology* (1995), vol. 5, no. 1: 27-31, 27. In this article, Hadlow also reviewed the history of the neuropathological investigations and noted that for sixty years after the work of Besnoit and Morel, essentially all observers fixated on the vacuoles in the diseased brains and failed to see other features now considered equally important. They approached the pathology with a theory-laden bias expecting to see vacuoles and not expecting (or seeing) other important features; see pages 28-30.

[353] Hadlow, "Kuru likened to scrapie: the story remembered," *Phil Trans*, 3644.

diseases.[354] A specialized veterinary pathologist focusing on scrapie research, Hadlow became the recipient of knowledge circulated by Gajdusek, and he then became the crucial, if serendipitous, link connecting the animal and human diseases. Quickly joining the international dialogue with his own contribution, Hadlow pointed out the long latency period and, based on the earlier work in sheep first done in France, suggested Gajdusek try inoculating material from kuru victims directly into the brains of primates, which would need to be watched for a long time.[355] Jay Ingram correctly reckons that Hadlow's letter "stands as a near-perfect example of the combination of scientific writing and thinking … short, sharp, and to the point … [listing] the similarities and [proposing] the crucial experiments."[356]

Gajdusek took Hadlow's advice and later stressed its importance, because, before this, "Infection had … seemed a very unlikely etiologic possibility for kuru."[357] He and Zigas had initially searched for evidence of transmissibility by attempting to transmit kuru by inoculating small lab animals in 1957 without any success. But now he began a series of inoculations using primates, and he understood the crucial importance of long-term observation. The information hypothesized by Sir John McFadyean that had helped the Frenchmen, Cuillé and Chelle, prove the transmissibility of scrapie had, thus, been circulated through time and space to Gajdusek via an American intermediary working in

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[354] William J. Hadlow, "Scrapie and Kuru," *The Lancet* (September 1959), vol. 274, no. 7097: 289-290.
William J. Hadlow, "Kuru likened to scrapie: the story remembered," *The Philosophical Transactions of the Royal Society*, Series B, Biological Sciences (November 27, 2008), vol. 363, no. 1510: 3644.
[355] Hadlow, "Scrapie and Kuru," *The Lancet* (1959), vol. 274, no. 7097: 289-290.
[356] Ingram, *Fatal Flaws*, 56.
[357] Gajdusek, "Kuru in New Guinea and the Origin of the NINDB Study of Slow, Latent, and Temperate Virus Infections of the Nervous System of Man," 3.

England. Gajdusek and Gibbs began a series of inoculations in 1963, and it was two years before the primates succumbed to whatever agent had been transmitted to them from the human kuru victims. The transmissibility and the long latency period were both confirmed.[358]

Suddenly, the understanding of kuru changed. After reluctantly discounting the possibility of an infectious encephalitis, Gajdusek and Zigas had originally considered it to be a 'degenerative disease of the central nervous system.'[359] With its transmission to primates, however, it became established as a contagious, transmissible disease. It was no longer a purely degenerative disease; nor was it a psychological reaction to sorcery, a disease of toxicity or deficiency, or a simple hereditary disease. Rather, it was immediately conceptualized anew into a transmissible disease with some, as yet, unknown causative agent, presumably viral, that could be communicated to other host animals. The scientific research of seven decades from the late nineteenth century to 1965, beginning with tobacco plants and sheep and culminating with the Fore people of New Guinea, exemplifies and underscores the importance of free and open scientific dialogue uncomplicated by social factors such as reputation, financial gain, or politics. It reveals how such research can, should be, and has been done. Not coincidentally, it also illustrates how successful it can be when done correctly and earned the 1976 Nobel Prize in Physiology or Medicine for D. Carleton Gajdusek for his work in defining the new concepts of slow viruses and slow viral diseases.

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[358] D.C. Gajdusek, C.J. Gibbs Jr., and M. Alpers, "Experimental Transmission of a Kuru-Like Syndrome to Chimpanzees," *Nature* (1966), vol. 209: 794-796.
[359] Gajdusek and Zigas, "Degenerative Disease of the Central Nervous System in New Guinea," *NEJM, 974-978.*

Discussion

Needless to say, Gajdusek continued his experiments trying to transmit kuru. He elaborated on them by using different animals and also trying to experimentally transmit other, poorly understood human diseases. Additionally, his inoculation experiments were augmented with oral feedings of infected materials, and he was able to infect monkeys though the oral ingestion of infectious material from scrapie-infected mice. Thus, he successfully induced scrapie to cross the species barrier to primates.[360]

Most importantly, in 1980, he was able to successfully transmit both kuru and CJD to primates by feeding them material from kuru and CJD victims. This essentially confirmed the now unanimous suspicion that kuru had indeed been transmitted during the ritual cannibalization of kuru victims among the Fore. It also linked kuru and CJD, despite the differences in their epidemiology and microscopic pathology: both were transmittable, and both were subacute spongiform encephalopathies. Moreover, it allowed for an explanation of the origins of kuru among the Fore. It now seemed probable that kuru had begun with a spontaneous case of CJD (incidence of about one case per million humans) that had arisen among the Fore. The victim's family members had unwittingly consumed the victim's body and brain and ingested the transmissible agent. Subsequently, the tribal custom of mortuary cannibalism continued the decades long epidemic of kuru among their kinsmen. The evidence that kuru was the result of a transmissible agent had allowed for a complete reconceptualization of the disease, easily

[360] Schwartz, *How the Cows Turned Mad*, 72.

explaining its etiology and the details of the epidemic. It also explained why the incidence of kuru was falling rapidly. Noticeably fewer cases were appearing, especially among the young children, because the cessation of the ritual feasting in the late 1950s had interrupted its continued propagation.

In the decades to follow, however, there would be new epidemics of TSE. Creutzfeldt-Jacob disease was inadvertently transmitted among a few humans during neurosurgical procedures by the use of specialized brain electrodes used to investigate epilepsy patients. It was also transmitted when corneas (and certain other intracranial tissues) of unsuspected CJD patients were transplanted into other patients.[361] Another small, limited epidemic resulted from the use of human growth hormone collected from human pituitary glands at autopsy; several hundred (mostly children) suffered terrible deaths, because some of the growth hormone lots were contaminated with the agent of CJD. The final epidemic, of course, was the mad-cow epidemic in Great Britain that killed several hundred in the United Kingdom, France, and a few other countries.

Gajdusek's work with kuru established this almost unique disease as the first recognized slow viral infection of the human nervous system, but it was obviously not the only one. Furthermore, there were numerous other puzzling diseases of the human nervous system of uncertain, or controversial, etiology. These included (among others) Alzheimer's disease, Huntington's chorea, Parkinson's disease, and the various demyelinating diseases such as multiple sclerosis. Some of these diseases are labeled

[361] During the 1970s, the author used human dura mater (the thick, protective covering layer overlying the brain), which had been harvested posthumously from German donors, to repair dura mater damaged beyond repair in severe head injuries. It was an excellent dural substitute, but it, too, was found to have transmitted several cases of CJD to the recipients before its use was stopped.

'degenerative diseases,' but this can be misleading, since aging itself is a degenerative process (as every octogenarian knows all too well) that seems to be part of the normal life cycle, not a disease in and of itself. Some of the pathological changes of Alzheimer's disease, for example, are present to a much lesser degree in the, apparently normal, aging brain, and the etiology of about 90% of Alzheimer's disease is unknown. About 10% of Alzheimer's disease is genetic, with patients apparently inheriting the disease as an autosomal dominant trait.

Interestingly, though, kuru and CJD had also been considered to be 'degenerative diseases' before it was realized they were transmissible, a characteristic that certainly seemed to distinguish them from other such degenerative diseases. That is, of course, unless the other diseases also proved to be transmissible. Gajdusek had redefined kuru and CJD as degenerative diseases secondary to a slow viral infection. He was confident he had "established that virus infections of man could, after long delay, produce chronic degenerative disease and disease with apparent heredofamilial patterns of occurrence."[362]

Moreover, he was immediately able to include within this category several other brain diseases somehow associated with viral infections. Subacute sclerosing panencephalitis (SSPE) is a rare, though not as rare as CJD, inflammatory disease of the brain associated with the measles virus; it is frequently fatal. Less frequently fatal and somewhat resembling the pathological picture of multiple sclerosis is acute disseminated encephalomyelitis; it, too, is associated with viral infections. Progressive multifocal

[362] D. Carleton Gajdusek, "Unconventional Viruses and the Origin and Disappearance of Kuru," Nobel Lecture, December 13, 1976. https://www.nobelprize.org/nobel_prizes/medicine/laureates/1976/gajdusek-lecture.pdf accessed January 20, 2018.

leukoencephalopathy (PML) is associated with a virus known as JC virus that is commonly found in the nervous system of healthy people; it seems to be activated and cause PML when a patient's immune system is compromised as, for example, in acquired immune deficiency disease syndrome (AIDS).

Naturally, Gajdusek wondered if Alzheimer's, Huntington's or Parkinson's or other diseases, might also be transmissible, might they also be degenerative diseases resulting from a chronic infectious agent (viral, prional, or otherwise)? Certainly, the label, 'degenerative disease, did not aid in understanding their etiology; in fact, it seems to obscure their etiology. His successful work with kuru and the transmission of CJD to primates encouraged Gajdusek to experiment further. Most of his efforts to transmit diseases such as Lou Gehrig's disease or multiple sclerosis failed, but his attempts to transmit Alzheimer's disease to primates were intriguing. He was unsuccessful in transmitting the disease using tissue taken from victims of sporadically occurring Alzheimer's disease, but he was successful in transmitting the inherited form of Alzheimer's to primates. Remarkably, the "diseases as transmitted to primates were clinically and pathologically typical subacute spongiform virus encephalopathies, and did not have pathological features of Alzheimer's disease in man."[363] So, the situation of familial Alzheimer's disease (about 10% of cases) seemed to be distinctly different from the sporadic disease. Unlike the sporadic disease, inherited Alzheimer's disease is transmissible and, like kuru or CJD, should be the result of a transmissible agent. The production of the spongiform changes characteristic of CJD, when the disease is transmitted to primates, suggests a similar (if not identical) agent but leaves open the

[363] Gajdusek, "Unconventional Viruses and the Origin and Disappearance of Kuru," Nobel Lecture, December 13, 1976.

question of why the different, non-spongiform pathological changes of typical Alzheimer's disease occur when the disease is inherited. This disparity also suggests that sporadic and inherited Alzheimer's disease may be two distinct entities rather than the same disease.

By the end of the twentieth century, more than four decades had passed since cannibalism had been abolished among the Fore, but occasional cases of kuru continued to appear. These late cases are attributed to the extremely long latency period of TSEs in humans that can sometimes exceed four decades. Such a very long interval between cause and effect will almost always complicate efforts to establish causation. If, for example, a victim cannot be connected to known vectors such as injections of human growth hormone, corneal transplants, the mad-cow epidemic in England, or some other well-recognized precipitating event, it will be extremely difficult to implicate an event that occurred decades earlier. Additionally, the incidence of sporadic Creutzfeldt-Jacob disease is only about one per million people, making sporadic CJD a very rare and isolated disease. Thus, it will be very difficult to prove, or disprove, whether it is truly 'sporadic' or whether it was contracted decades earlier by an activity as mundane and commonplace as having a hamburger.[364] With respect to the transmissible spongiform encephalopathies, the old adage, 'the more we learn about them, the less we seem to understand them,' seems to be especially true.

These are clearly important issues for our understanding of these diseases, especially in humans. What we know developed over time, and it was worked out

[364] Approximately 90% of cases of CJD are considered sporadic; about 10% occur within families in what is generally thought to be an autosomal dominant pattern of inheritance.

through a truly international scientific discourse that resulted in scientifically constructed biomedical knowledge. The decades-long scientific discussion beginning with scrapie and ending with kuru, examined in this essay, clearly illustrates the importance of debate and the sharing of information in the creation of new biomedical knowledge. Clearly each of the research groups benefited from the work of its antecedents, and each contributed something of value to its successors. By 1960, a novel and useful conceptualization of scrapie and its causative agent had been developed, and it explained numerous, previously puzzling, aspects of both. There was disagreement, but on the whole, it was a remarkably collegial and international effort.

Because Kiheung Kim actually devotes the great majority of his excellent monograph to the period after 1960, the present narrative adds to the historiography of early research into the spongiform encephalopathies by extending and complementing Kim's work. Kim is also more interested in the social construction of disease, and the internalist view of the scientific research, presented in this paper, adds another dimension to his work. In fact, I would argue that the period examined here is better suited to this internalist approach examining the actual norms of scientific research. On the other hand, the period after the 1970s, though beyond the scope of this essay, may better lend itself to examination through the lens of social history for three reasons. In the first place, the last quarter of the century was a time of social history in the making. Social forces such as civil rights, minority rights, feminism, sexual liberation, and social activism, etc. seemed to overshadow the more traditional historical forces, such as economics, intellectual currents, politics, diplomacy, and warfare. Second, and largely because of this first circumstance, the last decades of the twentieth century saw the rise of social history, as a

strand of historiography, to such a position of dominance that it has upstaged and almost eclipsed the older notions of economic, diplomatic, and intellectual history. Third, the history of the conceptualization of the slow virus after the Nobel Prize of 1976 is marked by conflicting scientific findings that were more clearly related to social factors than to scientific factors. Social issues having little or nothing to do with careful observation, rational analysis, and meticulous, reasoned construction of scientific theories began to affect the creation of scientific knowledge, especially biomedical knowledge, in the last decades of the twentieth century to a greater and greater extent.

Thus, many historians of science and medicine may find it easier to approach the understanding of concept of the prion during the last quarter of the century from the standpoint of the sociology of scientific knowledge, at least until scientists resolve some of the present controversies. In fact, some, if not most, of these controversies have depended more on social disputes than on differences of scientific opinion. Because it examines the earlier and more scientific period, this thesis demonstrates how rational and productive scientific knowledge was produced in first three quarters of the century. It was a time when scientific knowledge was more often developed within the scope of the scientific method and through free and open exchange of information. There was markedly less interference from the more social aspects so increasingly involved in the creation of new scientific knowledge during the closing quarter of the twentieth century.

At the beginning of the twentieth century, the virus had been defined as a filterable and ultramicroscopic infectious agent, and when scrapie was shown to be transmissible, it was assumed to be a viral disease. However, knowledge of already known viral diseases, such as smallpox and measles hampered the investigation of

scrapie. Because this older paradigm included only those viral infections with relatively acute and short courses, scrapie did not fit neatly within this older conception of viral diseases. Scientists' theory-laden approach to scrapie was dominated by the older paradigm, and in order to incorporate scrapie into a viral category of disease, it was necessary to enlarge the paradigm of viral disease. This was done using the new, previously unconsidered alternative of the slow viral disease, a disease that developed over years, not days or weeks.

Over the course of the first half of the century, this quality of being able to produce slow infections over many years was added to explain the newly understood latency of scrapie. Thus, the concept of the slow virus was developed to explain new empirical evidence that was not characteristic of the better-known viruses typified by an acute illness. Because of the presence of DNA (or RNA) in viruses, the concept of the slow virus easily explained the different varieties of scrapie and would later explain other strain variations among other TSEs. By the middle of the twentieth century, this new category of slow viral disease was absorbed into the more general concept of viral disease. Moreover, the conceptualization of the transmissible agent of scrapie as a slow virus would function for several decades after 1960 to account for the long latency and variability of the disease. Even more importantly, the slow virus would be linked to other diseases affecting not just sheep but humans. Naturally, the grisly affects of these diseases on the human brain naturally magnified the fear of slow viral diseases such as kuru, mad-cow disease, Creutzfeldt-Jacob disease, and other human varieties of the spongiform encephalopathies. More importantly, though, the possibility that the understanding of the diseases and their transmissibility might elucidate important aspects

of other, more common diseases magnified the importance of understanding the spongiform encephalopathies.

If the agent were a slow virus, it would be expected to contain nucleic acids, and this genetic material would readily account for the observed tendency of slow viruses to mutate into different strains with more or less virulence. The adaptability of nucleic acids would also account for the observed differences in the signs and symptoms of the infectious diseases produced. Within a few years, though, this explanatory framework would be complicated and seriously challenged by radiobiological research that suggested nucleic acids were not a component of the scrapie agent.[365] This was confounding because nucleic acids are the usual way biologists explain the differences and the variability in different strains of disease organisms. In fact, without the presence of nucleic acids, it becomes extremely difficult, if not impossible, to adequately explain the different varieties of scrapie, and the empirically observed differences among the various TSEs.[366] So, a fundamental conflict in the scientific findings developed and was greatly magnified by social forces, and this conflict is a major reason why the later narrative of scrapie research is well served by Kim's social constructionist methodology.

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[365] Tikvah Alper, and W.A. Cramp, "Does the Agent of Scrapie Replicate Without Nucleic Acid?" *Nature* 214 (May 20, 1967): 764-766. See also, Tikvah Alper, "The Nature of the Scrapie Agent," *Journal of Clinical Pathology* 25, supplement 6 (January 1972): 154; and, Kim, *The Social Construction of Disease: From Scrapie to Prion*, 50-64.

[366] See for example, Bruce, M.E., "Scrapie Strain Variation and Mutation," *British Medical Bulletin* 49, no. 4 (October 1993): 822-838; and Bruce, et al., "Transmissions to Mice Indicate that 'New Variant' CJD is Caused by BSE Agent." See also, Lasmézas, Corinne, I., Deslys, Jean-Philippe, *et al.*, "Transmission of the BSE Agent to Mice in the Absence of Detectable Abnormal Prion Protein," *Science* 275, no. 5298 (January 17, 1997): 402-405. See also, Jeffrey Almond and John Pattison, "Human BSE," *Nature* 389, issue 6650 (October 1997): 437-438.

That is, there almost seems to be some fundamental inadequacy of the scientific method and its ability to reconcile conflicting evidence about the TSEs after 1960.

I would submit, however, that there has *not* been an inherent problem with the scientific method, which has served science so well and for so long. Rather, it is more likely that the important inconsistencies that have developed will ultimately be explained as they were explained during the earlier period examined in this essay, through diligent scientific investigation. The narrative presented here has revealed a combination of problems, some of which were due to theory-laden approaches to empirical data. Researchers initially misinterpreted observations, because their perception was biased by previous theories and beliefs. Other problems required adjustment of a paradigm in order to properly account for anomalies in the empirical data. However, those adhering to an older paradigm may contest such adjustments and resolution may take decades. This is not a problem with the scientific method; it is really an attribute. Resistance to change prevents scientific theories from being too easily discarded, and many, if not most, scientific anomalies will be satisfactorily resolved within the current theory if not hastily discarded. There is also the structural problem of underdetermination, which is greatly magnified by Kyle Stanford's elaboration of the fundamental stumbling block created by unconceived alternatives: "we have repeatedly been able to conceive of only a single theory that was well supported by all of the available evidence when there were indeed alternative possibilities *also* well supported."[367] When scientists cannot visualize a potential agent, it is very difficult to conceive of alternatives to the already known and characterized agents of disease transmission.

[367] Stanford, *Exceeding Our Grasp: Science, History, and the Problem of Unconceived Alternatives*, 21.

Importantly, though, the early evolution of scientific knowledge about slow viruses as etiologic agents of animal and human disease was relatively free of social influences. It was primarily a scientific endeavor undertaken by scientists, and it was primarily based upon their interpretations of the scientific method of the time. Moreover, through their communications, they created an international dialogue and shared information in order to advance the scientific understanding of disease causation. The greater part of this dialogue preceded the late twentieth-century philosophical conception of the social construction of scientific knowledge by decades, even generations. In fact, the sociological interpretation of the history of scientific knowledge really began about the time that twentieth-century social movements, such as feminism and the American civil rights movement, began to bring about the entrance of women and minorities into academic history programs in the 1960s.[368] Not only were they more interested in social history, they were far better trained in social history than they were in the fields of science or medicine.[369]

This accelerated the 'social turn' in the history of medicine, and critics argued it would produce 'medical history without the medicine,' or that the core narrative in the history of medicine (i.e. the construction of medical knowledge) would be lost in the thickets of social history. As early as 1980, it was being argued that recent scholarship in the history of medicine was neglecting "questions of clinical medicine, of the biology of disease, and of science, *even when such questions had a direct bearing on the particular*

[368] Joyce Appleby, Lynn Hunt, and Margaret Jacob, *Telling the Truth About History* (New York: W.W. Norton & Company, 1994), 146-152.
[369] Olga Amsterdamska and Anja Hiddinga, "Trading Zones or Citadels? Professionalization and Intellectual Change in the History of Medicine," in *Locating Medical History: The Stories and Their Meanings*, eds. Frank Huisman and John Harley Warner (Baltimore: Johns Hopkins University Press, 2004): 237-261, 241ff.

historical subject."[370] Not coincidentally, at about the same time there was a surge in efforts of various social groups to actually influence the development of scientific knowledge as women and African Americans, in particular, began to look to their own understanding of how medical science applied to their social groups.[371]

Toward the end of the twentieth century, however, various social forces conspired to significantly affect the production of scientific knowledge in ways that inhibit the unencumbered exchange of knowledge in an open and unrestricted dialogue. In *The Panic Virus*, historian of Science, Seth Mnookin, has examined this phenomenon with respect to the controversy surrounding the understanding of the role of childhood vaccinations in the etiology of autism.[372] His research clearly shows the profound influence social groups can have on the development of scientific knowledge and how profoundly misleading such non-scientific influence can be. He brings to light a sort of 'scientific' demagoguery that can persuade social groups to embrace and champion fallacious notions. He also demonstrates how misapprehension can be abetted by the mainstream press in its own quest for stories of social interest, even at the expense of objectivity and scientific fact. In *Pink Ribbon Blues*, medical sociologist, Gayle Sulik, approaches the misleading role of social influences from a different angle: financial interest.[373] In her estimation, the financial interests of doctors, medical instrument

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[370] Leonard Wilson, "Medical History Without Medicine," *Journal of the History of Medicine and Allied Sciences* 35, issue 1 (January 01, 1980): 5-7, 6. Italics added for emphasis.
[371] Ilana Löwry, "Historiography of Biomedicine: 'Bio,' 'Medicine,' and In Between," *Isis* 102, no. 1 (March 2011): 116-122, 119-121.
[372] Seth Mnookin, *The Panic Virus: A True Story of Medicine, Science, and Fear* (New York: Simon & Schuster, 2011).
[373] Gayle Sulik, *Pink Ribbon Blues: How Breast Cancer Culture Undermines Women's Health* (Oxford: Oxford University Press, 2011).

companies, and women's advocacy groups collaborate to distort the scientific knowledge of breast cancer to coincide with their own aspirations and goals.

Research into the nature of the etiologic agent of the transmissible spongiform encephalopathies continues, and the history of scrapie research suggests it should adhere to the principle of free, open, and unfettered scientific dialogue. As far as possible the scientific method should be insulated from various sociological factors, which are unlikely to increase the precision of research. Otherwise, if allowed to influence scientific research, such non-scientific factors such as inequitable funding, personal authority, reputation, and especially potential, or real, financial gain may be expected to diminish the importance of the scientific norms of research, and ultimately diminish the accuracy of scientific theories.

Bibliography

Almond, Jeffrey, and John Pattison, "Human BSE." *Nature* 389, issue 6650 (October 1997): 437-438.

Alper, Tikvah, "The Nature of the Scrapie Agent," *Journal of Clinical Pathology* 25, supplement 6 (January 1972): 154.

Alper, Tikvah and W.A. Cramp, "Does the Agent of Scrapie Replicate Without Nucleic Acid?" *Nature* 214 (May 20, 1967): 764-766.

Amos, Linda A. and John T. Finch, "Aaron Klug and the Revolution in Biomolecular Structure Determination." *Trends in Cell Biology* 14, no. 3 (March 2004): 148-152.

Amsterdamska, Olga and Anja Hiddinga. "Trading Zones or Citadels? Professionalization and Intellectual Change in the History of Medicine." In *Locating Medical History: The Stories and Their Meanings*, edited by Frank Huisman and John Harley Warner, 237-261. Baltimore: Johns Hopkins University Press, 2004.

Anderson, Warwick, *The Collectors of Lost Souls*. Baltimore: Johns Hopkins University Press, 2008.

Anonymous, "The Report of the Paris medical faculty." In *The Black Death*, translated and edited by Rosemary Horrox. Manchester: University of Manchester Press, 1994.

Anonymous, "Virus." In *Chambers's Encyclopedia: A Dictionary of Universal Knowledge for the People,* vol. IX. London: W. and R. Chambers, 1868: 810.

Anonymous, "E.E. Klein, M.D., F.R.S." *British Medical Journal* 1 (February 21, 1925): 388.

Anonymous, "Sir Stewart Stockman, M.R.C.V.S." *British Medical Journal* 1, issue, 3414 (June 12, 1926): 1017.

Anonymous (presumably Sir John McFadyean), "The Late Sir Stewart Stockman." *Journal of Comparative Pathology and Therapeutics* 39, no. 2 (June 30, 1926): 164-165.

Anonymous, "Obituary: Professor S.H. Gaiger, F.R.C.V.S." *Journal of Comparative Pathology and Therapeutics* 47 (January 1934): 330.

Appleby, Joyce, Lynn Hunt, and Margaret Jacob, *Telling the Truth About History*. New York: W.W. Norton & Company, 1994.

Baur, Erwin, "On the Etiology of Infectious Variegation." (1904) In *Phytopathological Classics*, Number 7. Translated by James Johnson. Ithaca: Cayuga Press, 1942: 55-62.

Bassi, Agostino, "Del Mal del Segno." (1835) In *Phytopathological Classics*, Number 10. Translated by P.J. Yarrow. Edited with introduction By G.C. Ainsworth and P.J. Yarrow. Baltimore: American Phytopathological Society, 1958, 1-49.

Beijerinck, M.W., "Concerning a Contagium Vivum Fluidum as a Cause of the Spot Disease of Tobacco Leaves." (1898) In *Phytopathological Classics*, Number 7. Translated by James Johnson. Ithaca: Cayuga Press, 1942, 33-52

Bennett, J.H., F.A. Rhodes, and H.N. Robson, "A Possible Genetic Basis for Kuru." *American Journal of Human Genetics* 11, no. 2 – part 1 (June 1959): 169-187.

Berndt, Catherine H., "Socio-Cultural Change in the Eastern Central Highlands of New Guinea." *Southwestern Journal of Anthropology*, 9, no. 1 (Spring, 1953): 116-117.

Berndt, Ronald, "A 'Devastating Disease Syndrome:' Kuru Sorcery in the Eastern Central Highlands of New Guinea." *Sociologus* 8, no. 1 (1959): 4-28.

Besnoit, J. and Ch. Morel, "Note sur les Lésions Nerveuses de la Tremblante du Mouton." *Revue Vétérinaire* 23 (1898): 397-398.

Bonomo, Giovanni Cosimo and Richard Mead, M.D., "An Abstract of Part of a Letter from Dr. Bonomo to Signor Redi, Containing Some Observations concerning the Worms of Humane Bodies," *Philosophical Transactions of the Royal Society (1683-1775)* vol. 23 (1702-1703): 1296.

Brody, Jacob A., William J. Hadlow, *et al*., "Soviet Search for Viruses That Cause Chronic Neurological Diseases in the U.S.S.R." *Science* 147, no. 3662 (March 03, 1965): 1114-1116.

Brown, Paul and Raymond Bradley, "1755 and all that: A Historical Primer of Transmissible Spongiform Encephalopathy." *British Medical Journal* 317 (December 1998): 1688-1692.

Bruce, M.E., "Scrapie Strain Variation and Mutation." *British Medical Bulletin* 49, no. 4 (October 1993): 822-838.

Bruce, M.E., Will, R.G., et al., "Transmissions to Mice Indicate that 'New Variant' CJD is caused by BSE Agent." *Nature* 389, issue 6650 (October 02, 1997): 498-501.

Burger, D., and G.R. Hartsough, "Transmissible Encephalopathy of Mink," in *Slow, Latent, and Temperate Virus Infections* edited by D. Carleton Gajdusek, Clarence J. Gibbs, Jr. and Michael Alpers, 3-12. Washington, US Public Health Service – NIH, 1965.

Burnet, Sir MacFarlane, *Natural History of Infectious Disease*. 3rd ed. Cambridge: Cambridge University Press, 1962.

Butler, P. Jonathon G. and Aaron Klug, "The Assembly of a Virus." *Scientific American* 239, no. 5 (November 1978): 62-69.

Carnevale, Franco, "Ramazzini, Bernardino." In vol. 4 of *Dictionary of Medical Biography*. Edited by W.F. Bynum and Helen Bynum. Westport: Greenwood Press, 2007: 1046-1049.

Carter, K. Codell, "Koch's Postulates in Relation to the Work of Jacob Henle and Edwin Klebs," *Medical History* 29, no. 4 (October 1985): 353-374.

Celsus, *On Medicine*. Volume II of Loeb Classical Library. Translated by W.G. Spencer. Cambridge: Harvard University Press, 1938.

Chandler, R.L., "Encephalopathy in Mice Produced by Inoculation with Scrapie Brain Material," *The Lancet* 1, issue 7191 (June 24, 1961): 1378-1379.

Chamberland, C. "Sur un Filtre donnant de l'eau physiologiquement pure," *Comptes Rendus de L'Academie des Sciences* 99 (1884): 247.

Chung, King-Thom, and Deam Hunter Ferris, "Martinus Willem Beijerinck (1851-1931)." *American Society for Microbiology News* 62, no. 10 (1996): 540-541.

Collard, Patrick, *The Development of Microbiology*. Cambridge: Cambridge University Press, 1976.

Cuillé, J. and P.-L. Chelle, "La Maladie dite 'Tremblante' du Mouton est-elle Inoculable?" *Comptes Rendus de L'Academie des Sciences* 203 (1936): 1552-1554.

Cuillé, J. and P.-L. Chelle, "La Tremblante du Mouton est bien Inoculable." *Comptes Rendus de L'Academie des Sciences* 206 (1938): 78-79.

Cuillé, J., and P.-L. Chelle, "La Tremblante du Mouton est-elle Determinée par un Virus Filtrable?" *Comptes Rendus de L'Academie des Sciences* 206 (1938): 1687.

Cuillé, J. and P.-L. Chelle, "Transmission Expérimentale de la Tremblante à la Chèvre." *Comptes Rendus de L'Academie des Science* 208 (1939): 1058-1060.

Cuillé, Jean and Paul-Louis Chelle, "Investigations of Scrapie in Sheep." *Veterinary Medicine* 34, no. 7 (July 1939): 417-418.

Dickson, Samuel Henry, "On Contagion." *The American Journal of the Medical Sciences* 18 (July 1849): 107-118.

Farquhar, Judith and D. Carlton Gajdusek, eds. *Kuru: Early Letters and Field-Notes from the Collection of D. Carlton Gajdusek.* New York: Raven Press, 1981.

Fischer, Ann and John L. Fischer, "Æetiology of Kuru," *The Lancet* 275, issue no. 7139 (June 25, 1960): 1417-1418.

Fischer, Ann and J. L. Fischer, "Culture and Epidemiology: A Theoretical Investigation of Kuru." *Journal of Health and Human Behavior* 2, no. 1 (Spring 1961): 16-25.

Fracastoro, Hieronymi *De Contagione et Contagiosis Morbis et Eorum Curatione, Libri III*. Translated and Notes by Wilmer Cave Wright. New York: G.P. Putnam's Sons; 1930.

Gaiger, S.H., "Scrapie." *Journal of Comparative Pathology and Therapeutics* 37 (January 1924): 259-277.

Gajdusek, D. Carleton, *KURU: Early Letters and Field-Notes from the Collection of D. Carleton Gajdusek.* Edited by Judith Farquhar and D. Carleton Gajdusek. New York: Raven Press, 1981.

Gajdusek, D. Carleton, "Kuru in New Guinea and the Origin of the NINDB Study of Slow, Latent, and Temperate Virus Infections of the Nervous System of Man," in *Slow, Latent, and Temperate Virus Infections* edited by D. Carleton Gajdusek, Clarence J. Gibbs, Jr. and Michael Alpers, 3-12. Washington, US Public Health Service – NIH, 1965.

Gajdusek, D. Carleton, "Unconventional Viruses and the Origin and Disappearance of Kuru," Nobel Prize Lecture, December 13, 1976. https://www.nobelprize.org/nobel_prizes/medicine/laureates/1976/gajdusek-lecture.pdf accessed January 20, 2018.

Gajdusek, D. Carleton, "Infectious Amyloids: Subacute Spongiform Encephalopathies as Transmissible Cerebral Amyloidoses," in, *Fields Virology*. Edited by B.N. Fields *et al*. Philadelphia: Lippincott-Raven, 1996.

Gajdusek, D.C., C.J. Gibbs Jr., and M. Alpers, "Experimental Transmission of a Kuru-Like Syndrome to Chimpanzees." *Nature* 209, no. 5025 (1966): 794-796.

Gajdusek, D.C. and V. Zigas, "Degenerative Disease of the Central Nervous System in New Guinea." *New England Journal of Medicine* 257 no. 20 (November 14, 1957): 974-978.

Garrison, Fielding H., *An Introduction to the History of Medicine*. 4th ed. Philadelphia: W.B. Saunders, 1929.

Genung, Elizabeth F., "The Development of the Compound Microscope." *Bulletin of the History of Medicine* 12 (1942): 576-579.

Ghesquier, Danièle, "A Gallic-Affair: The Case of the missing Itch-Mite in French Medicine in the early Nineteenth Century." *Medical History* 43, no. 1 (January 1999): 26-54.

Gill, O Noel, Yvonne Spencer, *et al*., "Prevalent Abnormal Prion Protein in Human Appendixes after Bovine Spongiform Encephalopathy Epizootic: Large Scale Survey." *British Medical Journal* 347, no. 7929 (19 October 2013): 11.

Glasse, Robert, "Cannibalism in the Kuru Region of New Guinea." *Transactions of the New York Academy of Sciences* 29, no. 6 (April 1967): 748-754.

Glasse, Robert and Shirley Lindenbaum, "Fieldwork in the South Fore: the process of ethnographic inquiry." In *Prion Diseases of Humans and Animals*, edited by Stanley Prusiner, John Collinge, John Powell, and Brian Anderson, 77-91. Chichester: Ellis Harwood, 1992.

Glassie, John *A Man of Misconceptions: The Life of an Eccentric in an Age of Change*. New York: Riverhead Books, 2012.

Gordon, W.S., "Advances in Veterinary Research: Louping-ill, Tick-borne Fever, and Scrapie." *The Veterinary Record* 58, no. 47 (November 1946): 516-525.

Grafe, Alfred, *A History of Experimental Virology*, Translated by Elvira Reckendorf. Berlin: Springer-Verlag, 1991.

Greig, J. Russell, "Scrapie: Observations on the Transmission of the Disease by Mediate Contact." *The British Veterinary Journal* 96 (1940): 203-206.

Greig, J. Russell, "Scrapie in Sheep." *The Journal of Comparative Pathology* [successor to *The Journal of Comparative Pathology and Therapeutics*] 60 (1950): 263-266.

Hadlow, William J., "Scrapie and Kuru." *The Lancet* 274, no. 7097 (September 1959): 289-290.

Hadlow, William J., "Neuropathology and the Scrapie-Kuru Connection." *Brain Pathology* 5, no. 1 (1995): 27-31.

Hadlow, William J., "Kuru likened to scrapie: the story remembered." *The Philosophical Transactions of the Royal Society*, Series B, Biological Sciences 363, no. 1510 (November 27, 2008): 3644.

Hippocrates, *Breaths.* In *Hippocrates*. Vol. II of Loeb Classical Library. Translated by W.H.S. Jones. Cambridge: Harvard University Press, 1923.

Hippocrates, *Nature of Man*. In *Hippocrates*. Vol. IV of Loeb Classical Library. Translated by W.H.S. Jones. Cambridge: Harvard University Press, 1931.

Hook, Robert *Micrographia* (Istanbul: e-Kitap Projesi & Cheapest Books, 2014).

Horzinek, Marian C., "The Birth of Virology." *Antonie van Leeuwenhoek*, 71, issue 1-2 (February 1997): 15-20.

Howard-Jones, Norman, "Fracastoro and Henle: A Re-Appraisal Their Contribution to the Concept of Communicable Diseases." *Medical History* 21, no. 1 (January 1977): 61-68.

Hughes, Sally Smith, *The Virus: A History of the Concept*. New York: Science History Publications, 1977.

Ingram, Jay, *Fatal Flaws: How a Misfolded Protein Baffled Scientists and Changed the Way We Look at the Brain.* New Haven: Yale University Press, 2013.

Ivanowsky, Dmitrii, "Concerning the Mosaic Disease of the Tobacco Plant." (1892) In *Phytopathological Classics*, Number 7. Translated by James Johnson. Ithaca: Cayuga Press, 1942, 27-30.

Johnson, James, "Erwin Baur," in *Phytopathological Classics*, Number 7. Translated by James Johnson. Ithaca: Cayuga Press, 1942: 53-54.

Johnson, Richard T., and Kenneth P. Johnson, "Slow and Chronic Virus Infections of the Nervous System." In *Recent Advances in Neurology*. Edited by Fred Plum. Philadelphia: F.A. Davis Company, 1969: 33-78.

Kim, Kiheung, *The Social Construction of Disease: From Scrapie to Prion*. New York: Routledge, 2007.

Klatzo, Igor, D.C. Gajdusek, and V. Zigas. "Pathology of Kuru." *Laboratory Investigation* 8, issue 4 (1959): 799-847.

Klein, E., "Infectious Diseases, Their Nature, Cause, and Mode of Spread I," *Nature* (March 5, 1891), vol. 43, no. 1114: 416-419

Klein, E., "Infectious Diseases, Their Nature, Cause, and Mode of Spread II," *Nature* (March 12, 1891), vol. 43, no. 1115: 443-446.

D.H. Kruger, *et al*., "Helmut Ruska and the Visualization of Viruses." *The Lancet* 355 (May 13, 2000): 1713-1717.

Kuhn, Thomas, *The Structure of Scientific Revolutions*. 4th ed., 50th Anniversary Edition, with an Introductory Essay by Ian Hacking. Chicago: University of Chicago Press, 2012.

Lasmézas, Corinne, I., Deslys, Jean-Philippe, *et al*., "Transmission of the BSE Agent to Mice in the Absence of Detectable Abnormal Prion Protein." *Science* 275, no. 5298 (January 17, 1997): 402-405.

Lechevalier, Hubert, "Dimitri Iosifovich Ivanovski," *Bacteriological Reviews* 36, no. 2 (June 1972): 135-145.

Lépine, P. "Sur le Virus Écossais de la Tremblante du Mouton (Louping Ill): Inoculation in Sheep." *Comptes Rendus des Séances de la Societé de Biologie et des se Filiales* 108 (1931): 397-399.

Liberski, P.P. and D.C. Gajdusek, "Kuru: Forty Years Later, A Historical Note." *Brain Pathology* 7, no. 1 (January 1997): 555-560.

Lloyd, G.E.R., *Early Greek Science: Thales to Aristotle*. New York: W.W. Norton, 1970.

Löwry, Ilana, "Historiography of Biomedicine: 'Bio,' 'Medicine,' and In Between." *Isis* 102, no. 1 (March 2011): 116-122.

Lucretius, *On the Nature of Things*. In Loeb Classical Library. Translated by W.H.D. Rouse. Cambridge: Harvard University Press, 1975.

Lustig, Alice and Arnold Levine, "One Hundred Years of Virology" *Journal of Virology* 66, no. 8 (August 1992): 4629-4631.

Major, Ralph H., "Agostino Bassi and the Parasitic Theory of Disease." *Bulletin of the History of Medicine* 26, no. 2 (July 1944): 97-107.

Marton, L., *Early History of the Electron Microscope*, With a Preface by Dennis Gabor, FRS. San Francisco: San Francisco Press, 1968.

Mathews, John D., Robert Glasse, and Shirley Lindenbaum, "Kuru and Cannibalism." *The Lancet* 2, issue no. 7565 (August 24, 1968): 449-452.

Mathiason, Candace K., et al, "Susceptibility of Domestic Cats to Chronic Wasting Disease." *Journal of Virology* 87, no. 4 (February 2013): 1947-1956.

Mayer, Adolf, "Concerning the Mosaic Disease of Tobacco." (1886) In *Phytopathological Classics*, Number 7. Translated by James Johnson. Ithaca: Cayuga Press, 1942, 11-25.

McFadyean, Sir John, "Scrapie." *Journal of Comparative Pathology and Therapeutics* 31, no. 2 (June 1918): 102-131.

McGowan, J.P., *Investigation into the Disease of Sheep Called "Scrapie" (Traberkrankheit; La Tremblante): with especial reference to its association with Sarcosporidiosis*. Edinburgh: William Blackwood and Sons, 1914.

McGowan, J.P., "Scrapie." *Journal of Comparative Pathology and Therapeutics* 31, no. 4 (December 2018): 278-290.

McGowan, J.P., "Iron Deficiency and its Possible Relationship to Human Disease." *Lancet* 204, no. 5282 (November 22, 1924): 1060-1061

McGowan, J.P., "Causation of Cancer." *The British Medical Journal* 1, no. 4029 (March 26, 1938): 698-699.

McKirahan, Richard D., *Philosophy Before Socrates: An Introduction with Texts and Commentary*. 2nd ed. Indianapolis: Hackett Publishing Company, 2010.

Mnookin, Seth, *The Panic Virus: A True Story of Medicine, Science, and Fear*. New York, Simon & Schuster, 2011.

Mudd, Stuart, "Filters and Filtration," in *Filterable Viruses*. Edited by Thomas M. Rivers. Baltimore, William & Wilkins Company, 1928.

Nutton, Vivian "The Seeds of Disease: An Explanation of Contagion and Infection from the Greeks to the Renaissance." *Medical History* 27, no. 1 (January 1983): 1-34.

Nutton, Vivian, "The Reception of Fracastoro's Theory of Contagion: The Seed That Fell among Thorns?" *Osiris* 6 (1990): 196-234.

Nutton, Vivian, "To Kill or Not to Kill? Caelius Aurelianus on Contagion." In *Text and Tradition: Studies in Ancient Medicine and its Transmission – Presented to Jutta Kollesch*, eds. Klaus-Dietrich Fischer *et al*. Leiden: Brill, 1998, 233-242.

Nutton, Vivian, *Ancient Medicine*. 2nd ed. London: Routledge, 2013.

Oxford English Dictionary, online edition (*Lancet* 15 June 1850: 711/1) http://www.oed.com/view/Entry/223861?redirectedFrom=virus#eid accessed October 31, 2016.

Oxford English Dictionary, online edition (*Lancet* 3 August 1940: 141/1) http://www.oed.com/view/Entry/223861?redirectedFrom=virus#eid accessed October 31, 2016.

Patterson, Robert, "Cases and Observations on the Molluscum Contagiosum of Bateman, with an Account of the minute Structure of the Tumours," *Edinburgh Medical and Surgical Journal* 56 (1841): 279-288.

Pattison, Iain, *John McFadyean: A Great British Veterinarian*. London: J.A. Allen, 1981.

Pekoc, K., “Obituary: William J. Hadlow.” *Veterinary Pathology* 52, no. 5 (August 2015): 985.

Porter, J.R., “Agostino Bassi Bicentennial (1773-1973).” *Bacteriological Reviews* 37, no. 3 (September 1973): 284-288.

Power, Henry and Leonard W. Sedgwick, *The New Sydenham Society’s Lexicon of Medicine and the Allied Sciences*, Vol. II. London: The New Sydenham Society, 1882. No pagination. https://archive.org/details/b21513685_0002 . Accessed August 29, 2017

Rivers, Thomas “Some General Aspects of Filterable Viruses.” In *Filterable Viruses*. Edited by Thomas Rivers. Baltimore: Williams & Wilkins, 1928: 55-94.

Rogers, Nancy G., M. Basnight, C.J. Gibbs and D.C. Gajdusek, “Latent Viruses in Chimpanzees with Experimental Kuru.” *Nature* 216, no. 5114 (November 04, 1967): 446-449.

Roncalli, R.A., “The History of Scabies in Veterinary and Human Medicine from Biblical to Modern Times,” *Veterinary Parasitology* 25, no. 2 (July 1987): 193-198.

Roos, Raymond, “D. Carlton Gajdusek.” *Proceedings of the American Philosophical Society* 159, no. 1 (March 2015): 101-4.

Scerri, Eric. *A Tale of Seven Scientists and a New Philosophy of Science.* Oxford: Oxford University Press, 2016.

Schwartz, Maxime, *How the Cows Turned Mad: Unlocking the Mysteries of Mad Cow Disease*. Translated by Edward Schneider with a new foreword by Marion Nestle. Berkeley: University of California Press, 2003.

Schneider, Kurt et al, “The Early History of the Transmissible Spongiform Encephalopathies Exemplified by Scrapie.” *Brain Research Bulletin* 77 (2008): 343-355.

Sigurdarson, Sigurdur “Epidemiology of Scrapie in Iceland and Experience with Control Measures,” in *Sub-acute Spongiform Encephalopathies: Proceedings of a Seminar in the CEC Agricultural Research Program*. Held in Brussels, 12-14 November 1990. Boston: Kluwer Academic Publishers, 1991.

Sigurdsson, Björn, “Maedi, A Chronic Progressive Infection of Sheep’s Lungs.” *The Journal of Infectious Diseases* 90, no. 3 (May-June, 1952): 233-244.

Sigurdsson, Björn, “MAEDI, A Slowly Progressive Pneumonia of Sheep: An Epizoological and Pathological Study.” *The British Veterinary Journal* 110 (1954): 255-270.

Sigurdsson, Björn, "RIDA, A Chronic Encephalitis of Sheep: With General Remarks on Infections Which Develop Slowly and Some of Their Special Characteristics." *British Veterinary Journal* 110, no. 9 (September 1954): 341-354.

Sismondo, Sergio, *An Introduction to Science and Technology Studies*, 2nd ed. Oxford: Blackwell Publishing, 2010.

Stanford, Kyle, *Exceeding Our Grasp: Science, History, and the Problem of Unconceived Alternatives.* Oxford: Oxford University Press, 2006.

Stanley, W. M., "Soviet Studies on Viruses." *Science* 99, no. 2564 (February 1944): 136-138.

Stockman, Sir Stewart, "Scrapie: An Obscure Disease of Sheep." *Journal of Comparative Pathology and Therapeutics* 26 (1913): 317-319.

Stockman, Sir Stewart "Letter to Major General Frederick Smith," (February 16, 1920), folder 'fs/3/2/49' in the Royal College of Veterinary Surgeons, London, England.

Stockman, Sir Stewart, "Contribution to the Study of the Disease Known as Scrapie." *Journal of Comparative Pathology and Therapeutics* 39 (1926): 42-71.

Straub, Otto Christian, "Maedi-Visna Virus Infection in Sheep: History and Present Knowledge." *Comparative Immunology, Microbiology, and Infectious Diseases* 27, no. 1 (January, 2004): 1-5.

Sulik, Gayle, *Pink Ribbon Blues: How Breast Cancer Culture Undermines Women's Health*. Oxford: Oxford University Press, 2011.

Temkin, Oswei, *Galenism: The Rise and Fall of a Medical* Philosophy. Ithaca: Cornell University Press, 1973.

Thucydides, *The Peloponnesian War*. Translated by Rex Warner. London: Penguin Books, 1954.

Wallis, George "Annual Oration, *Delivered March 8th*, 1790, Before the Medical Society, Bolt Court, Fleet Street, London." London: G.G.J. and J. Robinson, M.DCC.XC, 32-33. http://find.galegroup.com.proxy1.library.jhu.edu/ecco/retrieve.do?sgHitCountType=None&sort=Author&tabID=T001&prodId=ECCO&resultListType=RESULT_LIST&searchId=R1&searchType=BasicSearchForm&currentPosition=1&qrySerId=Locale%28en%2C%2C%29%3AFQE%3D%28A0%2CNone%2C13%29George+Wallis%3AAnd%3ALQE%3D%28da%2CNone%2C4%291790%3AAnd%3ALQE%3D%28BA%2CNone%2C124%292NEF+Or+0LRH+Or+2NEK+Or+0LRL+Or+2NEI+Or+0LRI+Or+2NEJ+Or+0LRK+Or+2NEG+Or+0LRF+Or+2NEH+Or+0LRJ+Or+2NEM+Or+0LRN+Or+2NEL+Or+0LRM%24&retrieveFormat=MULTIPAGE_DOCUMENT&userGroupName=balt85423&inPS=true&contentSet=ECCOArticles&&docId=CW3308249320&retrieveFormat=MULTIPAGE_DOCUMENT&docLevel=FASCIMILE&workId=CW3308249320&relevance

PageBatch=CW108249320&showLOI=&contentSet=&callistoContentSet=ECLL&docPage=article&hilite=y accessed November 20, 2016.

Washburn, S. L., "The New Anthropology." *Transactions of the New York Academy of Sciences* 13 issue 7, series II (May 1951): 298-304.

Waterson, A.P. and Lise Wilkinson, *An Introduction to the History of Virology*. Cambridge: Cambridge University Press, 1978.

Wilkinson, Lise "The Development of the Virus Concept as Reflected in Corpora of Studies on Individual Pathogens." *Medical History* 21, no. 1 (January 1977): 15-31.
Wilkinson, Lise, "Rinderpest and Mainstream Infectious Disease Concepts in the Eighteenth Century." M*edical History* 28, no. 2 (April 1984): 129-150.

Wilson, Leonard, "Medical History Without Medicine." *Journal of the History of Medicine and Allied Sciences* 35, issue 1 (January 01, 1980): 5-7.

Worboys, Michael, *Spreading Germs: Disease Theories and Medical Practice in Britain, 1865-1900*. Cambridge: Cambridge University Press, 2000.

Zigas, V. and D.C. Gajdusek, "Kuru: Clinical Study of a New Syndrome Resembling Paralysis Agitans in Natives of the Eastern Highlands of Australian New Guinea." *Medical Journal of Australia* 11, no. 21 (November 23, 1957): 745-754.