ONE

A Ferret's Sneeze

THE RISE OF THE GERM THEORY of disease in the second half of the nineteenth century played a crucial role in the history of modern medicine, contributing to a major transformation in the medical understanding of the normal and the pathological. When researchers made invisible colonies of microbial organisms responsible for a number of illnesses, a fundamental change in the medical understanding of disease occurred. Microbiologists, as Georges Canguilhem convincingly argues, conceived of the difference between the normal and the pathological as a difference of *kind* rather than *degree*, in contrast to the common medical understanding. They thus rejected the physiological thesis generally adopted in the nineteenth century that pathological phenomena were largely identical to corresponding normal phenomena "save for quantitative variations."[1] The experimental identification of microbial organisms as causative agents of communicable diseases supported the microbiologists' conception of the normal and the pathological, along with their distinctive view of the sick body. A human body invaded by a thriving colony of invisible germs inevitably constituted a different kind of body. "It is not normal for a healthy subject," Canguilhem laconically remarks, "to have diphtheria bacilli lodged in his throat."[2]

The difference between the normal and the pathological condition was not a quantitative but a qualitative difference, a difference not of degree but of kind, according to microbiologists at the turn of the twentieth century. The experimental investigation of infectious diseases in the laboratories of the late nineteenth and early twentieth centuries was essential to articulating an ontological conception of infectious disease as a specific condition with a specific cause, which in turn contributed significantly to a more general trend in the scientific description of disease. The reification of disease as an entity

separate from the patient reduced the question of illness to a matter of infection, symbolized by the suggestive image of invisible germs invading healthy bodies.

This chapter explores the process of disease reification in the case of influenza. Focusing on the first half of the twentieth century, it argues that scientists stabilized the influenza virus as the specific cause of disease only to see that stability crumble over the following decades. The ontological conception of the normal and the pathological disclosed a biological entity that was elusive and erratic.

IN THE REALM OF THE INFINITELY SMALL

Beginning in the 1890s, microbiologists applied existing bacteriological methods to influenza, trying to confirm the assumption that it was an infectious disease caused by a contagious agent. However, attempts to cultivate the pathogenic agent that was presumed to be responsible for influenza were confounded by a peculiar circumstance. The careful examination of nasal mucus gathered from hospital patients in the midst of seasonal flu outbreaks invariably revealed the presence of multiple bugs—a whole range of unexpected bacterial residents—in the depths of the human body.[3] "In a malady in which the secondary invaders give character to a large majority of the severe cases, it is to be expected that many different organisms should be described," wrote Hans Zinsser in a review published in 1922.[4] The growing number of bacterial organisms cultured in liquid media and visualized by means of histological staining transformed the task of identifying the cause of the "sweating sickness," as it was known in popular discourse, into a real challenge. What was the cause of influenza?

At the turn of the twentieth century, many microbiologists concluded that one particular suspect, Pfeiffer's bacillus, was responsible for the seasonal nuisance. However, to the great frustration of the scientists, the experimental exposure of laboratory animals to Pfeiffer's bacillus never quite consistently reproduced the typical signs of the illness: a runny nose, a rising temperature, and a relentless cough. Researchers could not agree on a bacterial agent and began to wonder if influenza might in fact constitute not a bacterial but a viral disease. Perhaps it was not a bacillus but a virus that was causing the notorious condition. Unfortunately, however, researchers then knew little about this biological entity.

Despite relentless attempts, microbiologists were initially unable to cultivate viruses in the laboratory; only bacteria grew well on artificial media. Nevertheless, they assumed that these viruses existed. Strictly speaking, viruses were not completely unknown. "It is true," remarked microbiologist Thomas M. Rivers in 1932, "that the exact nature of these agents is unknown, but to say that the agents themselves are unknown is somewhat of an exaggeration."[5] Rivers reasoned that "in order to know an infectious agent it is not essential to see it."[6] In fact, scientists conceived of the virus as a special group of biological things precisely because they could not be seen. The limits of the bacteriological regime of representation and intervention established a horizon of possibility, in which the figure of the virus gradually emerged as a negative correlate of existing scientific practices. In the early twentieth century the concept of the virus referred to an obscure object defined primarily in negative terms. Bigger than chemical molecules but smaller than bacterial cells, the virus not only escaped the gaze of the most powerful optical microscope available at the time but it also passed the physical barriers of the finest filters. The virus, moreover, also failed to grow on the lifeless media typically used by microbiologists in their laboratories. These mysterious microbes, it turned out, were so minute that conventional methods developed for bacteria could not make them grow. The figure of the virus thus appeared at the periphery of the bacteriological laboratory and its methods of microbe farming.

In a 1931 article, Sir Henry Hallett Dale summarized the three cardinal properties that characterize a virus as "invisibility by ordinary microscopic methods, failure to be retained by a filter fine enough to prevent the passage of all visible bacteria, and failure to propagate itself except in the presence of, and perhaps in the interior of, the cells which it infects."[7] As Dale's brief summary shows, the three distinctive properties defining the virus concept at that time were predicated on the deployment of a number of practices and were formulated exclusively in negative terms. The three properties represented an embarrassing number of technical inabilities: first, the inability to render the virus visible by optical microscopes; second, the inability to retain the virus by porcelain filters; and third, the inability to cultivate the virus in lifeless media. For the microbe farmers, the virus constituted a challenge. Since the virus could not be seen by existing microscopy methods, new ones had to be invented; since it could not be grown by conventional culture techniques, new ones had to be developed; since filtration lacked accuracy, new forms of filtration had to be conceived.[8]

At the turn of the twentieth century, the virus thus emerged as a strange and subtle entity, seeping, in the most literal sense of the word, through a finely woven fabric of technical contraptions designed to capture and culture the smallest biological things that make up the natural world. Paradoxically, the virus came into view as a unique object precisely because it escaped standard efforts conceived to make it concrete. Initially, its prime quality was its profound obscurity. This tiny little entity proliferating ambiguously at the existential polarities of life and death challenged the celebrated power of the modern laboratory and its methods of microbe farming. Microbiologists perceived these limitations as technical problems to be overcome.

This chapter explores how microbiologists brought the disease inside the laboratory and transformed the biological entity that was too small to be seen into an object suitable for experimental research. It follows in the footsteps of recent science and technology studies and highlights the essential role of scientific practices in the stabilization of a historically specific object of concern in the investigation of infectious disease. These scientific practices allowed microbiologists to substantiate the existence of the virus, characterize its structure, and affirm the authority of the laboratory. A distinctive set of knowledge practices made the invisible agent concrete: The virus became detectable, maintainable, manipulable, and transferable. However, what researchers revealed was not the virus itself, but the trace that it left after it had entered susceptible bodies. Exploring the signs and symptoms of experimental infection, microbiologists began to know more about the virus without really seeing it.

The production of scientific knowledge and the accumulation of experimental evidence were important for the social, cultural, and political salience that the virus gained as an object of concern over the following decades. The new concept of influenza as a viral disease increasingly underpinned medical approaches and public health programs in the twentieth century. The concept was also crucial for the constitution of virology as a new specialty of medical research, allowing microbiologists to devise new diagnostic techniques, develop new forms of treatment, and make predictions about pandemics. The challenge for microbiologists was to establish the virus as a legitimate cause of disease, carve out virology as a promising field of medical research, and establish the significance and relevance of the virus for clinical medicine and public health.

As historian Ton van Helvoort pointed out, the ontological understanding of the normal and the pathological "assumed that influenza is caused by a specific agent."[9] Unable to render it visible by means of optical microscopes or to cultivate it on artificial growth media, microbiologists eventually turned their attention from cause to effect. Scientific claims about the existence of invisible microbes as the cause of infectious diseases would become credible once scientists were able to reproduce the effect of a viral infection in the laboratory. If not the virus itself, researchers hoped to see at least the result of its presence, evidenced by the typical signs and symptoms of infection.[10] However, this strategy of tracing the virus through signs and symptoms faced the fundamental difficulty that the cause did not always produce a recognizable effect. How, then, was it possible to identify the virus despite the irregular character of infection? What kind of medical concepts, scientific practices, and experimental forms of life did the microbe farmers need to mobilize for the proper signs and symptoms to appear and authorize the ontological understanding of influenza as a disease triggered by the invasion of an invisible germ?

The first successful isolation of an influenza virus derived from a human population is generally believed to have been achieved in 1933 by Wilson Smith, Christopher Howard Andrewes, and Sir Patrick Playfair Laidlaw at a farm of the National Institute of Medical Research at Mill Hill, a suburb on the outskirts of London.[11] In a celebrated set of experiments that immediately aroused the "greatest interest among medical men," as an article carried by the *New York Times* phrased it at the time, the British scientists were able to accomplish what many had attempted before to no avail; namely, to infect experimental animals in the laboratory with the pathogenic agent suspected to be responsible for epidemics in human populations.[12]

The experimental infection of an animal body in the laboratory constituted, of course, a crucial cornerstone of "Koch's postulates," which define the necessary criteria (isolation—cultivation—inoculation) for a microbe to be accepted as the causative agent of a contagious disease.[13] The procedure that the British scientists followed was relatively simple and straightforward: In the midst of a regular outbreak of seasonal influenza in London in 1933, Smith, Andrewes, and Laidlaw received a battery of vials containing human mucus—derived from nasal and throat washings—gathered by a doctor from hospital patients. First, the scientists filtered the mucus, which they either

FIGURE 7. Can we beat influenza? With the help of an assistant, Christopher Andrewes injects a dose of the influenza virus into the nose of a sedated ferret. Original publication in *Picture Post*, "Can We Beat Influenza?" February 2, 1946. Photo by Kurt Hutton. Copyright: Getty Images.

dropped into the noses or injected into the muscles of several animal species (almost everything from mice to monkeys).[14] All experiments failed, except those conducted with ferrets. By the second day after infection, as the British scientists noticed, the ferrets were remarkably quiet and they also looked ill. By the third day, they were yawning, and they developed a fever that

was typical of human infection. "The ferrets are sneezing!" Laidlaw cheerfully exclaimed.[15] The animals, in other words, revealed the characteristic symptoms.

Although the 1933 attempt was primarily designed to isolate the virus by transmitting the microbe from one host to another, the crucial challenge was to render the illness visible as a trace of the viral infection. Many scientists, in fact, had already tried a number of times to transmit the suspected but invisible agent to various animal species in the artificial environment of the laboratory. They all failed, either because the symptoms were not specific enough, or they were vague and variable, or because the animals were not susceptible to the pathogenic agent in the first place. The ferret became a successful laboratory animal for the microbe farmers and their attempt to confirm the virus as the single cause of disease primarily because it produced signs of illness that were strikingly similar to the clinical symptoms of influenza typically observed in the hospital setting. The ferrets were generative not so much because they manifested some kind of sickness, but rather because they manifested the *proper form* of the illness. They produced the characteristic symptoms: The ferrets were not only sneezing but also their temperature was rising and their noses were running. The disease, in other words, assumed a particular form. The pathological effect became effective and provided compelling evidence because it took the right shape in a framework of visibility that was constituted by the clinic and that relied on the set of symptoms observed in humans.[16] The experimental infection of these animals faithfully reproduced the illness, with all its symptomatic characteristics that physicians had witnessed in patients. To understand how the microbe farmers succeeded, we must now look more closely at the peculiar nature of the bodies that the British scientists used in their celebrated experiments.

SIR PATRICK'S FERRETS

In his 1865 *Introduction to the Study of Experimental Medicine,* the French physiologist Claude Bernard argues that the clinic should be considered "only as the entrance to scientific medicine, . . . [the] first field of observation which a physician enters: but the true sanctuary of medical science is a laboratory; only there can he seek explanations of life in the normal and pathological states by means of experimental analysis."[17] In Bernard's view, the physician must rely on the laboratory and the animal body to achieve true medical sci-

ence. Only there, in the laboratory, will the persistent physician finally be able, with the assistance of an animal model of disease, to account for "what he has observed in his patients."[18]

As Bernard's programmatic account indicates, the emergence of experimental medicine entailed two important shifts: from the clinic to the laboratory and from the human body to the animal body.[19] According to historian Ilana Löwy, the use of animal bodies "was established in the nineteenth century, as an extension and codification of older medical practices."[20] Yet the physiologists' provocative claim that laboratory studies conducted on animal bodies were indispensable to the scientific understanding of human diseases was not completely accepted until the field of microbiology emerged. Indeed, Löwy underscores in her account that it was microbiology itself that finally placed the animal body at the heart of scientific medicine. Investigations conducted by microbiologists, Löwy notes, "vindicated and enlarged earlier proposals to ground diagnosis, therapy and prevention of diseases in laboratory-based research, and firmly linked the fate of sick individuals to that of laboratory animals."[21]

Laboratory animals had already played a crucial role in the scientific research pursued by the microbe farmers Louis Pasteur and Robert Koch and their coworkers in France and Germany. These animals were used not only to isolate bacterial organisms but also to examine their pathological effects with the hope of producing vaccines to fight the battle against germs. Concomitantly, however, this incredibly generative form of knowledge-practice also raised the problem of generalization. What was the medical significance of a scientific fact derived from an experimental test conducted on an animal body? How was it possible to generalize from an artificially generated animal disease to a naturally occurring human condition? Animal experimentation was thus confronted with the difficult problem of aligning the animal's fate with those of humans and, by implication, those of humans with those of animals. How did the microbe farmers achieve this alignment in the case of influenza?

In his essay on scientific experimentation in animal biology, Canguilhem observes that "nothing is as important for a biologist as his choice of material to study."[22] Biologists in general and microbiologists in particular decide to work with specific animal bodies for distinctive reasons. In the case of influenza, the choice was indeed profoundly structured by the need to find an animal species that manifested the symptoms of illness typically observed in the clinic. These symptoms allowed scientists to represent the experimental

disease in a clinical frame and thus align the animal with the human pathology.[23] Significantly, the clinical frame of reference that the British scientists mobilized to persuade doctors of the existence of an invisible germ was both enabling and disabling. But before we explore this paradoxical moment in the making of an experimental fact, we must first examine the particular kind of animal life that played such an essential role in the early history of influenza's scientific investigation. It was a particular variety of ferrets that allowed microbe farmers to isolate the virus in the laboratory, establish it as the cause of disease, and describe it in concrete terms.

Smith, Andrewes, and Laidlaw succeeded in their experiments by and large because they worked with the ferret, a domesticated relative of the weasel. As it turned out, this particular species was the "right tool for the job."[24] The ferret represented the right species because it was able to elicit the "right" effect and generate credible evidence. The scientists were able to produce the *same* symptoms in a *different* body and thus align the animal's disease with the human condition and link the laboratory with the clinic. But why was the ferret so well placed to ferret out these compelling facts? Why was it able to produce the proper symptoms? How was the occurrence of asymptomatic infections avoided? To ask the question in a slightly different way: How did the ferret *become* such a valuable testing body for the reproduction of signs that could link the animal's disease with the human condition? What the answers to these questions highlight are the inevitable contingencies that characterize scientific research. These contingencies contributed to the emergence of an ontological understanding of infectious disease as a specific entity with a specific cause that was essential for establishing microbiology's authority as a scientific discipline concerned with the control of epidemics.

In early 1933, Smith incidentally learned about an outbreak of influenza among the staff of the Wellcome Laboratories in London. Apparently, some ferrets housed there for another research project also came down with the flu. This seemed to suggest that transmission between animal and human bodies had occurred. Ironically, as the scientists realized much later on, the ferrets had not actually caught the flu, but dog distemper, an extremely infectious disease affecting the dog populations of the British aristocracy. The disease was known to cause similar symptoms.[25] Misreading these symptoms for influenza, Smith suggested to Andrewes and Laidlaw that they set up a test to explore if ferrets were indeed susceptible to the disease, as appeared to be the case. Significantly, however, the British scientists succeeded not only because they decided to work with ferrets but also, and perhaps primarily, because they

were able to work with a particular *variety* of ferrets. Coincidentally, Laidlaw was raising ferrets at the farm of the National Institute for Medical Research for his work on dog distemper. This research had been made possible by a large financial contribution provided by *The Field* magazine, a British sporting weekly.[26] Laidlaw's original interest, however, was not in distemper itself, but in the flu. In fact, he only chose to focus on distemper, a highly contagious disease characterized by fever, nasal discharge, coughing, and loss of appetite, in the hopes that this research would ultimately lead to a better understanding of influenza.[27] Laidlaw thus worked on one disease with another firmly in mind. But despite the similar symptoms, the two diseases were not related at all, as Laidlaw eventually realized. The observation of symptoms was simply not reliable enough for an accurate diagnosis. Nevertheless, the laboratory animal that he had picked for his experimental work on dog distemper unexpectedly turned out to be a perfect model for the flu.

As Laidlaw's colleague Sir Henry Hallett Dale remarked, "An effective method of prophylaxis or treatment would be enthusiastically welcomed by all who bred or kept dogs for sport or companionship."[28] Because of the affective investment of the British not in people suffering from seasonal flu, but in hounds plagued by dog distemper, a group of scientists at the National Institute for Medical Research, headed by Laidlaw, found themselves in a comfortable position to conduct extensive research and to design, manufacture, and maintain a costly technical infrastructure. This, in turn, contributed in no small part to the success of the first experimental transmission of the influenza virus from human to animal bodies. Not surprisingly, the ability to work with uninfected animal bodies, carefully bred and kept in complete isolation, was critical for identifying the unknown cause of a regularly occurring, rapidly spreading, highly infectious disease. Constituting the influenza virus as a unique causative agent, as a concrete biological entity, required—literally—the construction of a living test subject susceptible to the disease and capable of consistently manifesting its clinical form.

ANTISEPTIC ECOLOGIES AND PURIFIED BODIES: THE ART OF FERRET BREEDING

To constitute themselves as masters of microbe farming and establish their expertise in medical matters, first the scientists had to learn the art of ferret breeding. The rise of the ferret as a productive animal model in influenza

research was thus not simply a work of nature. To establish a working experimental system and make the virus visible as a trace, the ferret had to be transformed into a productive body. This transformation highlights the challenges of experimental research, revealing the type of practices that were required for microbiologists to produce compelling facts about a contagious disease. The ferrets Laidlaw had raised since 1926 for his investigation of dog distemper were of a very particular breed.[29] They were immunologically naïve, raised through several generations and under conditions of complete isolation. They were housed in a special building with a floor "constantly covered with a Lysol bath three inches deep," a costly technical feature that Laidlaw proudly noted.[30] Each experimental animal was placed in a cage, which was itself placed in a cubicle. Before entering the isolation facility, a "sanctuary of sterility," workers clothed in rubber boots and rubber coats were carefully cleaned head to toe with Lysol, a common disinfecting solution.[31] Barred from any contact with the outside world, the ferrets found themselves inhabiting a peculiar form of life. They lived in a separate ecological sphere entirely removed from the natural history of infectious disease. It was this rather unusual form of life, generated primarily for experimental purposes, that produced the "right" signs of illness, bypassed the complications of asymptomatic infections, and thus successfully linked the animal with the human disease. As a result, scientific understandings of influenza increasingly came to depend on how this body responded to the virus.

The ferret was neither inexpensive nor particularly easy to handle. In fact, scientists frequently complained that the animals were aggressive and inflicted painful injuries with their sharp teeth. The body of the ferret also came with a large and costly infrastructure to keep animals alive, making it difficult for scientists to produce facts about the virus. Paradoxically, the successful *promotion* of infection required the successful *prevention* of infection. Once the seminal separation of virus and its designated host had been achieved through the strict observation of tedious rules of isolation and containment, the experimental encounter evinced the desired effect. To the great satisfaction of all, Sir Patrick's ferrets were highly susceptible to the influenza virus; they were yawning and sneezing, their temperature was rising, and their noses were running. They had great trouble breathing and they had a "splendid nasal catarrh."[32] As historian Michael Bresalier shows in his detailed account of the British research group, this form of animal testing not only enabled scientists to reproduce the typical signs of illness in the laboratory but it also facilitated the deployment of a clinical mode of measurement—the fever chart—as a

FIGURE 8. A ferret in the cage. Image of a ferret during scientific experiments on the influenza virus. Original publication in *Picture Post*, "Can We Beat Influenza?" February 2, 1946. Photo by Kurt Hutton. Copyright: Getty Images.

visual means of representation.[33] Significantly, this clinical mode of measurement, as Bresalier suggests, rendered the experimental disease legible in a conventional frame that was familiar to doctors.

It is no coincidence that these animal experiments were immediately followed by a series of human experiments—though the latter were not always the result of meticulous planning.[34] Immediately after the successful infection of ferrets with an influenza virus, Smith, Andrewes, and Laidlaw made two consecutive attempts to transmit the invisible agent back from ferrets to humans to establish an even firmer link between the animal and the human disease. However, these experiments failed, most probably because the volunteers had already become immune to the viral strain circulating in London at the time. Just as it was hard to find a susceptible animal body, it was difficult to find a susceptible human body in the context of an explosive epidemic. The invisible virus was everywhere, making accurate scientific research difficult. "Man," Laidlaw observed, "is an exceedingly bad experimental animal and almost useless . . . during an epidemic."[35] However, a consequential incident occurred in early March 1933 while Wilson Smith was inspecting a couple of infected ferrets at the farm. "A ferret with sick, tired eyes and misery in his bones" gazed at the scientist standing over

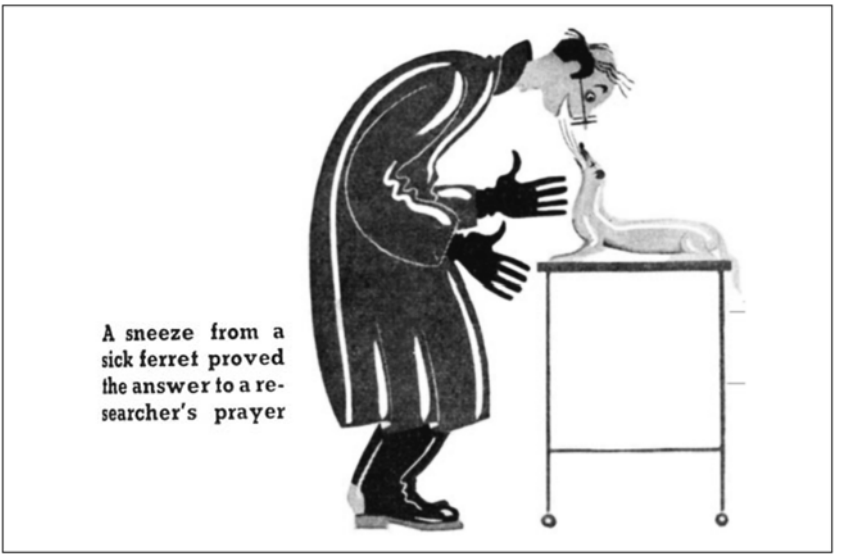

FIGURE 9. The answer to a prayer. A ferret accidentally infecting a researcher in the microbiological laboratory. Drawing by George De Zayas in J. D. Ratcliff, "Cold Comfort," *Collier's Magazine*, February 26, 1938.

him.[36] Unexpectedly, the animal sneezed right in Smith's face; soon thereafter, the microbe farmer came down with the flu.[37]

Unintentionally, the seamless circulation of contagious matter meticulously engineered in the sanctuary of experimental research was suddenly put into reverse, enabling the accidental performance of another test.[38] Despite this awkward moment of medical science temporarily out of control, the researcher dutifully collected the sticky secretions that his body released and requested that his colleagues filter the mucus and drop a few milliliters of the fluid back into the nose of a healthy ferret. A few days later, the animal looked miserable. By accident, the experimental isolation of the influenza virus had come full circle. Now the bodies of the microbe farmers had become victims of their own farming practices, which was perceived as the ultimate confirmation that the virus grown in the laboratory was indeed "human." A ferret's sneeze provided "the tip-off to the biggest question about influenza that remained to be answered," reported an article in a popular magazine.[39] The British scientists termed the strain derived from Wilson Smith "WS"; it was dried, bottled, frozen, and passed on to collaborating laboratories in the United States and Australia. It eventually became one of the classic strains

of influenza research, reproduced endlessly in laboratories all over the world. Animating hundreds of experimental studies conducted by generations of scientists, the strain was praised for its unique plasticity; it was exceptionally amenable to laboratory work. It remained remarkably generative, surviving the most drastic technical manipulations to become the triumphant emblem of a scientific discipline on the rise.

HOW THE LABORATORY UNDERMINED THE CLINIC'S DIAGNOSTIC AUTHORITY

In his account of the scientific investigation of plague, Andrew Cunningham shows that the ascendancy of the laboratory fundamentally transformed the identification and representation of infectious disease.[40] At first sight, it might seem as if the microbe farmers simply added a causal model to an existing clinical syndrome, but this addition operated as a true supplement, prompting a reconfiguration of the classification of disease over the following years. The experimental tracing of microorganisms and their conceptualization as causal agents of communicable diseases had a significant impact on the definition of pathological entities; it fundamentally changed the conditions under which a disease is determined. Scientists and journalists have largely overlooked this important transformation in the identity of infectious disease. Popular accounts have presented the rise of the laboratory primarily in terms of ambitious scientists unveiling a hidden nature, discovering the true causes of disease.[41] But these accounts have fundamentally misconceived the tremendous impact of the science, because experimental research did not merely unveil the cause of disease: It changed the very identity of the disease.

In the case of influenza, the identification of the pathogenic agent in the laboratory was initially predicated on a symptomatological concept of the pathological. Although microbe farmers were well aware from other infectious diseases that there are no "true" symptoms of a disease, the influenza virus only became recognizable as a credible cause once a laboratory animal faithfully manifested the "true" symptoms as they were commonly observed in the clinic. Experimental work was conducted under the assumption that "if the initial association between the micro-organism and the disease was a correct one, the inoculated animal would develop the very same disease."[42] But as soon as the "true" symptoms of the disease, as observed in humans, manifested themselves in the ferret body, it increasingly became obvious that

no true symptoms actually existed that would unmistakably identify the disease. When Smith, Andrewes, and Laidlaw began to infect mice with the strain that they had just transmitted successfully to ferrets, they discovered that it was possible to make these ubiquitous laboratory animals susceptible to the virus. However, in mice they could detect neither a rising temperature, nor a runny nose, nor a stubborn cough.[43] In fact, almost no reactions, with the exception of weight loss, were recognizable.[44] Were these animals "sick"? And if they were sick, was it the very same disease? Whatever condition the scientists observed in infected mice, it was hardly recognizable as the flu.

The isolation of the virus in the laboratory was bound to subvert the clinical identification of the disease on which the scientific research was predicated. As microbe farmers quickly realized, the *same virus* did not necessarily produce the *same symptoms* in all animal species. Analogies of clinical form, therefore, were not particularly reliable when it came to the determination of a disease in a particular species. As we now know, many animal species are in fact susceptible to the influenza virus, but their bodies are biologically constrained to produce *different* symptoms. Even though chickens are readily susceptible, these animals would not have been a successful model in the laboratories of the early twentieth century because they would have failed to manifest the symptoms typically observed in the clinic. In chickens, influenza presents itself not only as a *respiratory* illness but also and primarily as a *gastrointestinal* condition. In contrast to ferrets, infected chicken neither sneeze, nor do their beaks run. In fact, many die without any visible symptoms. This lack of visible symptoms would make it difficult, if not impossible, to authorize the animal model and link it with the human disease. What scientists once used to call "fowl *plague*" in the early twentieth century only became "avian *influenza*" (and thus the very same disease) once they began to classify infectious diseases on the basis of a *causal* model rather than a clinical *syndrome*.[45] Today's prophetic proclamations about avian influenza as the cause of a human pandemic have thus become possible only due to the ontological understanding of the normal and the pathological that microbiologists established: It is also contingent on the tests that they developed in the laboratory.

When the causal model was added to the clinical syndrome, it slowly began to operate as a supplement, increasingly displacing the diagnostic value of the clinical gaze and prompting a fundamental change in the identity of disease.[46] This model recognized the diagnostic authority of the clinic, only to subvert it. The disease was made different from itself, turning

into a new pathological entity defined primarily in the laboratory in terms of causative agents, and not in the clinic in terms of symptoms. Paradoxically, the identification of the cause of the disease fundamentally changed its identity, bringing about a comprehensive process of redefinition and reclassification.

The constraints of clinical form, to use a modified term borrowed from Marilyn Strathern, were thus both enabling and disabling for the microbe farmers.[47] The isolation of the influenza virus in ferrets became possible on the basis of a form of evidence, which rendered impossible the conception that fowl *plague* and avian *influenza* actually represent the very same disease (with different symptoms). The identification of the influenza virus in the laboratory constituted a moment of both recognition and misrecognition. Similar to other cases of infectious disease, the reproduction of the "true" symptoms of influenza in the laboratory enabled scientists to recognize that there are actually no true symptoms.[48] Instead the symptoms depend on the species and their bodies. As long as the isolation of the virus in an animal body and its authorization as a causative agent were predicated on the faithful reproduction of the human syndrome in an animal body, it was predicated on a mistaken model. The scientific claim about the microbial cause of the contagious disease was authorized within the context of a clinical definition of the condition, which the microbiological practice of growing bugs and testing bodies was bound to undermine.

As a disease, influenza has always been notoriously difficult to diagnose. "Clinical findings . . . are not particularly useful for confirming or excluding the diagnosis of influenza," a review published in the Clinician's Corner of the Journal of the American Medical Association recently emphasizes.[49] On the basis of symptoms, a reliable medical judgment is often impossible, except in the context of larger epidemics with multiple cases and similar symptoms. But in the absence of such an epidemic, it has remained difficult for physicians to make an accurate diagnosis. In fact, influenza has entirely disappeared as a diagnostic entity in the clinical context. Physicians are instructed to automatically classify all respiratory diseases as "influenza-like illness." As this notion already indicates, cases of influenza-like illness look like the flu in terms of their symptoms, but they actually might have other causes and might not even be flu. What physicians diagnose today, therefore, is a syndrome. They thus acknowledge that only a test in the laboratory can unmistakably identify the disease and distinguish it from respiratory illnesses that mimic influenza's symptoms.

Over the course of the twentieth century, the microbiological laboratory has thus shattered the clinic's diagnostic authority, introducing a series of powerful tests for the recognition of the pathological condition. Today, it is the laboratory—not the clinic—that is presumed to be the site where influenza is ultimately identified. The lab is perceived as the place where the disease comes into view in its "naked truth," where it shows its "actual nature," where its "real cause" is determined. "You don't really know you have the flu unless you have lab confirmation," an epidemiologist once told me. This shows how the laboratory has become the final arbiter in the world of influenza. Now everything can seem secondary to what laboratory workers say. The practice of growing bugs and testing bodies has allowed microbiologists to create a new concept, laboratory-confirmed influenza, and to talk with much more authority about the disease than physicians in the clinic ever could.[50] Today, the detour through the laboratory has become inevitable not only for patients and physicians but also for journalists and politicians. The very possibility of microbiology as a discipline is contingent on the constitution of its founding object. Microbiology's authority—its ability to produce compelling evidence about the contagious disease and make prophetic predictions about the future course of events—is inextricably bound up with the method of microbe farming, with the ability to characterize viruses, with the ability to grow them under controlled conditions, with the ability to inject them into laboratory animals, and with the ability to modify, manipulate, and reshape them. The masters of microbe farming are able to claim expertise in medical matters because of the microbial natures that they are culturing in their test tubes. These natures have provided microbiologists with a powerful position from which to speak with conviction about a modern dream: the eradication of infectious disease.

"THE GREATEST EXPERIMENT": IN SEARCH OF A VACCINE

Inspired by the work of the British scientists, the International Health Division of the Rockefeller Foundation identified influenza as a major field of research in 1934. Funded by a Rockefeller grant, Thomas Francis Jr. ordered laboratory animals and isolated an influenza virus, confirming the work of his British colleagues. He then embarked on a systematic search for a protective vaccine.[51] In 1936, Paul de Kruif, a former Rockefeller biologist and author

of *Microbe Hunters*, boldly told readers of the *Country Gentleman* that American scientists were about to conquer the flu.[52] "Studies were undertaken," Francis wrote around the same time in an internal research report, "to determine whether the artificially cultivated virus could be administered safely to human subjects and whether vaccination would elicit the production of antibodies in the serum of the subjects so treated."[53] These preliminary studies were conducted with research staff at the International Health Division in New York. No adverse reactions or disease symptoms were observed. Francis subsequently consulted Simon Flexner, director at the Rockefeller Institute of Medical Research, to arrange for the enrollment of volunteers in larger immunization studies. A consent form was drafted to allow Rockefeller researchers to introduce into willing participants' bodies "by one or more inoculations or otherwise, the virus of influenza regardless of the manner in which and of the source from which such virus shall have been obtained."[54] The form's main purpose was to release the Institute and the researchers from future liability claims based on potential injuries caused by an invisible virus whose structure and function were almost completely unknown to the scientists. Most volunteers were students at New York University's medical school. Admitted to the hospital of the Rockefeller Institute, participants in the trial were isolated in a special ward before they were immunized with an active virus that had been modified and manipulated in the laboratory.

Over the following years, a considerable number of clinical studies were carried out in the United States. Microbe farmers increasingly perceived seasonal epidemics as proving grounds for experimental vaccines; they were working with the virus while waiting for the next opportunity to vaccinate volunteers. Morris Siegel and Ralph Muckenfuss of the Bureau of Laboratories of the New York City Health Department initiated a series of trials, supported by a financial contribution provided by the Metropolitan Life Insurance Company. These trials were conducted in Letchworth Village, a New York state mental institution. Prison inmates in California were also sprayed with infectious substances that came out of the test tube. The problematic institutional context of these trials and the complete lack of human subject protection allowed scientists and officials to conduct "natural experiments" and keep participants under close surveillance. However, none of the studies, Francis concluded, "gave evidence that the vaccination had any significant effect against the natural disease."[55]

The outbreak of World War II injected a new sense of urgency into the development of an effective vaccine, especially in the United States. During

the great pandemic of 1918, the virus had traveled with the U.S. Army across the Atlantic, disrupting military operations, infecting troops, and killing thousands of soldiers. The military's growing concern about a repetition of that pandemic transformed the production of a protective vaccine into a matter of great importance and strategic advantage.[56] A magazine report published in 1941 portrayed influenza as a disease more dangerous for the U.S. military "than bombs."[57] In the same year, the Army's Board for Investigation and Control of Influenza and Other Epidemic Diseases established the Commission on Influenza and charged its members to propose concrete measures against the contagion. Headed by Thomas Francis, the commission included the country's most eminent researchers, including Rockefeller's George K. Hirst. Mobilizing authorities of civilian and military medicine, it "led a crash program to control influenza during the war, and it would remain the focus of American influenza research for twenty years."[58] The military considered influenza a "war disease," made substantial financial resources available for scientific studies, and increasingly shaped the course of experimental research in the United States.

In 1942, eight thousand individuals in two institutions in Michigan were immunized with a vaccine, but there was no epidemic to determine its efficacy. A subsequent, even more extensive trial was carried out the following year. Students at universities across the country were exposed to an inactivated strain. An epidemic of influenza started in November and lasted for several weeks. As Francis reported, "it was the first clear-cut demonstration that subcutaneous vaccination had actually created a significant difference between vaccinated and control groups in the course of a natural epidemic of disease."[59] On the basis of this trial, the Commission on Influenza recommended that the U.S. Army vaccinate all members of the armed forces. A comprehensive vaccination program for military personnel was designed and implemented toward the end of the war, in 1945. The program was based on a combination of civilian and military medicine. Vaccination against influenza worked, and the tide was turning—or so it seemed.

A MOVING TARGET

In February 1947, military doctors at Fort Monmouth, an army training camp in New Jersey, witnessed an epidemic among young recruits. A few months earlier, doctors had noticed a sharp rise in respiratory illness among American

troops stationed in Japan and Korea. Although clinically mild, these outbreaks of influenza were nonetheless perceived as exceptional for two reasons. First, the virus responsible for the disease was difficult to identify in the laboratory, and second, the promising vaccine introduced a few years earlier by the U.S. Army turned out to be almost completely ineffective both in the armed services and among the general public, where it was used after 1945.[60] To the considerable consternation of the microbe farmers, the protection, which had been so effective previously, suddenly seemed to fail completely. As it turned out, the virus was difficult to identify because it differed substantially from strains that had circulated earlier. Significantly, these older strains had also been used for the production of the vaccine.[61] Confronted with a striking failure of immunization, microbiologists suggested that a new strain of the virus had caused the 1947 outbreak. Due to the significant shift in the structure, the new strain was eventually designated as a new subtype of the influenza virus and was thus set apart from viruses that had been spreading before 1947. A certain degree of variation among influenza viruses had been noticed before, but never had such a substantial change been observed. It came as no surprise, then, that the 1945 vaccine barely protected the army's immunized troops.

The spectacular success of the vaccine introduced in 1945 was thus short-lived. John Eyler notes that the failure "forced researchers to reconsider the growing evidence of antigenic variation and challenged the model of the virus that had been taken for granted."[62] Researchers initially suggested that antigenic variation was irrelevant for the production of an effective vaccine, but they were wrong. Over the following years, microbe farmers became increasingly concerned with the changing nature of the virus, and they began to study the extent of the variation more systematically. The virus that they had been growing in the laboratory and preserving in the test tube turned out to be a biological thing living in time. Researchers recognized that they could not simply ignore this observation. They wondered whether the change was regular or irregular and whether the variation was finite or infinite. A regular change and a finite variation, they reasoned, would make protection by immunization possible and practical. Yet the more change and the more variation they detected, the less likely they were to produce a successful vaccine and eradicate the disease. The plasticity of the virus, its ability to infect bodies and accommodate changing environments, allowed microbe farmers to transfer the virus to the laboratory, but it also made it difficult for them to develop an effective vaccine. The microbe was a living thing, a moving target

that was less stable than it seemed when it was isolated for the first time. As Fred Davenport, Thomas Francis's colleague and successor as director of the Army's Commission on Influenza, noted, the ability of the virus to change "implies that the future of vaccination against influenza should consist of an endless series of crash programs designed to capture, bottle, and distribute each new minor antigenic villain as he mounts the stage."[63] Facing an elusive biological entity, microbe farmers worried that their attempts to control the disease were bound to be too slow and too late: The conquest of the disease was far from close. The vaccine provided a momentary sense of success, but its failure raised new questions about the ontological status of the virus.

BORROWED LIFE

"The man in the street," remarked French microbiologist and Nobel prize winner André Lwoff in a 1957 lecture, "generally considers viruses as the dangerous agents of infectious diseases."[64] Certainly this common understanding of the characteristic nature of viruses is not completely mistaken. But it is not here, in the popular perception of infectious diseases and their presumed causes, where the real danger lies. The real danger, Lwoff proposed in his third Marjory Stephenson Memorial Lecture, actually lies with the scientists. If one systematically studies their publications to better understand the concept of the virus, one gradually reaches, Lwoff observed, "a sort of feeling of the possible existence of some slight theoretical misunderstandings amongst virologists in which it may be dangerous to be involved." At stake, according to the microbiologist, is a crucial, "highly treacherous" notion: the notion of life.[65]

The purpose of Lwoff's lecture was to address the hotly contested nature of viruses. The ontological status of the virus remained a source of heated debate in microbiology. Some microbe farmers, among them several prominent influenza researchers, were convinced that viruses were living organisms, biological entities with basic characteristics of living things.[66] Others, by contrast, felt that viruses should primarily be considered inert chemical molecules. A third group, Lwoff noted, suggested that "statements that viruses are small organisms should be regarded with as much suspicion as statements that they are simply molecules."[67] But if viruses are neither living organisms nor inert molecules, what is their nature? What kind of things are viruses if they are neither living biological entities nor dead chemical substances?

What is the place of these peculiar bodies in the order of nature, and what is their relation to other biological forms of life? "My ambition," declared Lwoff in his lecture, "is to show that the word virus has a meaning." Tackling the problem of the nature of viruses in the hope that there was a definite answer to the question, Lwoff offered an oracular response: "Viruses should be considered as viruses because viruses are viruses."[68]

At the time of Lwoff's lecture, in the late 1950s, a large number of viruses had been isolated in the laboratory. It had increasingly become possible to measure these minute microbial things with a fair degree of accuracy, and some had even been crystallized and rendered visible by means of powerful microscopes.[69] Viruses were chemically purified in the centrifuge and were grown outside the animal body in chicken eggs and tissue cultures. They were dried and stored without significant loss of their pathogenic properties and had thus become available as objects of experimental research over a long period of time. Not surprisingly, the relevant scientific literature expanded exponentially in these decades.

Yet with all the knowledge, an observer remarked in 1938, "it is still not possible to pronounce with certainty on the nature of these agents." What kind of thing are viruses? How can they be defined? "Despite the fact that the solution of this question is not material to the study of most virus problems, it is of such abiding interest that virus workers continue to search for the answer."[70] By the end of the 1950s, as Lwoff's lecture indicates, the microbe farmers were still discussing the question.

The ambiguous place of the virus in the order of nature and the difficulty in deciding whether it is an animate or inanimate entity were due to the fact that the virus manifested some characteristics of living beings. As Edwin Lennette underscored in a 1943 article, "because the infectious agents classified as viruses possess the capacity to multiply or reproduce, because they showed marked specificity under natural conditions for certain hosts and tissues, are able to adapt themselves to new environmental conditions and to undergo variation, it is customary to regard them as living organisms."[71] The fact that viruses can multiply rapidly and adapt systematically to changing circumstances suggests that they are living things. The fact, however, that they can multiply, mutate, and adapt only in the presence of living cells suggests that they are not autonomous organisms. Furthermore, viruses are also unable to perform essential metabolic functions.

Lwoff's enigmatic response—considering viruses as neither living organisms nor small molecules—was inspired by the emerging vision of molecular

biology. Viruses, according to Lwoff, are unique. They are "infectious, potentially pathogenic, nucleoproteinic entities possessing only one type of nucleic acid, which are reproduced from their genetic material, are unable to grow and to undergo binary fission, and are devoid of a Lipmann system."[72] The purpose of Lwoff's definition of the modern concept of the virus was to resolve the problem of the nature of viruses by foregrounding the uniqueness of these strange entities in the order of nature.

Ever since microbiologists began investigating viruses in the laboratory as discrete objects that can be known, they have struggled with the peculiar nature of these entities. David Napier notes that microbiologists tend to ascribe notions of agency, mobility, and intentionality to viruses precisely because there is no straightforward answer to the ontological question.[73] The construction and stabilization of a complex material infrastructure for the generation and reproduction of microbial matter made the virus concrete as an object of scientific investigation. This infrastructure not only facilitated the cultivation of microorganisms but also simultaneously provoked the fundamental ontological question: What kind of things are viruses? In this chapter, we have seen how researchers established a complex experimental system, creating a fertile ground for the scientific examination of the influenza virus and the control of infectious disease at the crossroads of civilian and military medicine. Reproducing viruses in an animal species raised specifically for this purpose, microbiologists refined their skills of microbe farming. This virtuosity in the practical art of growing bugs and testing bodies was indispensable for the kind of expertise they claimed. What microbiologists revealed at the threshold of the living and the nonliving turned out to be an organic entity with a potential for life, a creature on the verge of the vital. The nature of this creature made it difficult for microbiologists to reproduce it under artificial conditions. The virus did not grow in the lifeless media of bacteriologists; it could not reproduce on its own and required the active support of a living body. Its life turned out to be contingent on someone else's life.

Galvanizing both the scientific and the popular imagination, the peculiar nature of the virus contributed to the growing fascination with the battle against infectious disease. As a material object, the virus provided a powerful foundation for the production of knowledge and the accumulation of facts. The pathogenic agent reached a threshold of positivity and made it possible for microbiologists to establish a testing ground for new forms of treatment and prevention. Challenging the clinic's diagnostic authority, the

laboratory turned into a privileged place and became the final arbiter for the determination of disease, allowing microbiologists to design strategies to control the contagion. It is important to note that the success of these strategies remained precarious ever since the virus was isolated for the first time. The ontological conception of the normal and the pathological and the constitution of the virus as the cause of disease established the dominance of the laboratory over the clinic, but they also prompted further questions about the nature of the microbial creature.

Microbe farmers stabilized the influenza virus as an object of scientific investigation only to see that stability crumbling. What scientists presented as a determining factor turned out to be a moving target that seemed to require a series of crash programs. The reduction of disease to the infectious agent ushered in a series of difficulties, complexities, and ambiguities that have troubled microbiologists ever since the influenza virus was first identified in the laboratory. Microbe farmers envisioned the virus as single decisive factor that would settle conclusively the identity of disease; it is the thing that ultimately determines whether a patient has flu or not. But this thing turned out to be so unstable und unreliable that it threatened to unsettle as much as it settled. The following chapters examine in more detail what it means to make an entity as elusive and erratic as the influenza virus the determining factor of disease. It was not the ontological conception of the normal and the pathological as such that inspired prophetic proclamations in the second half of the twentieth century. What made this mode of speech effective were the ambiguities that microbiologists encountered in the pursuit of their ontological conception. Scientifically inspired prophecy, pronounced by charismatic personalities with institutional authority, arose as an important response to scientifically generated ambiguity. The promise of prophetic appropriation was disambiguation. "This is how it is . . ."

In February 1938, *Collier's Magazine*, a popular American weekly featured a report on recent achievements in the microbiological investigation of influenza. "What does all of this mean to you?" the article queried. "Simply this: that research men . . . have flu on the run."[74]