Reality and politics in the war on infectious diseases

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"Inventing AIDS." "Constructing cancers." Relax; no bioterrorist mischief is implied. Like "Construction of nature," "Social construction of illness," "Social construction of scientific facts," and many others, these are titles of scholarly books and projects in science, technology, and medicine studies. They express a fashion shared by doctrines loosely known under the rubric of postmodernism. It is recognizable by the frequent scare quotation marks around words such as truth, reality, scientific, and objectivity. The scare quotes convey the message that scientific knowledge is so permeated by politics and cultural biases that it cannot be true and any claim to objectivity is illusory.

Take for example the 1894 identification of *P. pestis*, the bacillus that causes bubonic plague. Most people consider it a scientific discovery that increases our knowledge about plague and how to deal with it. Postmodernists scoff at the notion of quote-unquote discovery, which they deem "bizarre." Instead, they insist it to be a "laboratory construction of plague" that ushered in a new disease, so "there is an unbridgeable gap between past 'plague' and our plague," which are "incommensurable." They specifically attack the notion of the bacillus as a natural causative agent of plague; nothing is natural, because "a cause is always the consequence of a long work of composition."[1]

Since the late 1990s, many scientists and scholars criticized postmodernism for confusing issues and misrepresenting science. Everyone agrees that scientific research processes are human enterprises replete with personal ambition, academic politics, financial interests, and social maneuvers of all kinds. They disagree about the characteristics of knowledge, especially the contents of natural science, which are results acquired through scientific research. Postmodernists maintain that the contents of natural science are themselves soaked through with cultural prejudices. Scientists disagree, arguing that scientific knowledge *about nature* and *about reality* has abstracted from most if not all cultural biases present in research processes. Postmodernists err in rejecting realism, deriding human cognition, and rolling together the process and result of research into an unwarranted sociological determinism.

This chapter examines a favorite topic of postmodern historians, the emergence of microbiology in the late nineteenth century, in particular research in the microbial causes of three diseases: anthrax, tuberculosis, and cholera. Microbiology is a worldly science born in a time of rapid social change, raging nationalism, and imperial rivalry. From its inception, it involves heavily in disease control with all its cultural and political ramifications. Its story would be most favorable to the construction of a "history of science" portraying "science" as all politics and no objectivity. Yet as we will see, even in this difficult case, scientists are right in maintaining the objectivity of microbiological knowledge.

Infectious diseases past and future

Microbiology and the struggle against infectious diseases are important in themselves; they affect the health and life of entire populations. Anthrax, bubonic plague, cholera, diphtheria, influenza, leprosy, smallpox, typhoid, typhus, tuberculosis, yellow fever, the list of contagious diseases runs on. The curse of civilization from its dawn, they played major roles in shaping the courses of history.[2]

Since mid nineteenth century, infectious diseases were retreating before the forces of vaccines, antibiotics, better nutrition and housing brought by economic development, and improved sanitation and other public health infrastructures. Suppression of infectious diseases accounted for about eighty percent of the rise in life expectancy. Smallpox, the Old World disease that decimated native populations of the New World when it arrived, was eradicated worldwide in 1977. In England and Wales, infectious diseases accounted for 59 percent of all disease deaths around 1850; it dropped to 13 percent in 1971. Similar trends obtained in other developed nations. Euphoric about impending victory, the U.S. Surgeon General told Congress in 1969 that time was ripe to "close the book on infectious disease."[3]

Yet nature has its own ways. In the 1980s, the HIV/AIDS pandemic hit like a tidal wave that would not recede. While new diseases caused by Ebola, West Niles, and SARS viruses emerged, old ones returned reinforced with mutated bacteria that are resistant to multiple antibiotic drugs. Worldwide in 2002, HIV/AIDS claimed 2.9 million lives, while three old killers – pneumonia, diarrhea, and tuberculosis – together claimed 7.5 million. Most cases occur in the developing world, but in this age of global travel, no one can afford complacency. The rebound of tuberculosis in New York City in the early 1990s took a billion-dollar campaign to suppress. Time is ripe to reopen the book and learn from history.[4]

The germ theory of diseases

An epidemic is a complex web of causal processes. Infecting agents – bacteria, viruses, and parasites – differ in characteristics, life cycles, and virulence. They evolve and adapt to changing environments such increasing presence of antibiotics. They spread by air, water, food, insect vectors, sexual contact, and other means with varying effectiveness in various natural and social environments. Some, such as SARS and West Nile viruses, reside mainly in animal reservoirs and occasionally jump to humans. Within a human body, microbes face intricate defensive and physiological responses that vary according to the person's genetic and physiological conditions. Some microbes succumb to the body's immune system. Others survive. Some survivors perform physiological functions and become symbiotic with their host. Others lie quiescent for years, perhaps forever, without causing symptoms. Still others cause disease or death.

People were ignorant of most processes in disease etiology for a long time. Nineteenth century proponents of the germ theory of diseases struggled to demonstrate at least four points:

1. Communicability: some diseases, including the most deadly ones at the time, are contagious and can pass from people to people, directly or indirectly.
2. Causality: the agents that spread the disease are not mere organic toxins but microbes.
3. Vitality: microbes do not generate spontaneously from inorganic matters; they are genuine living organisms that multiply only by reproduction from their kind.
4. Specificity: microbes come in a variety of species, and a specific species of microbe causes a specific disease.

Although obvious today, each point was highly contentious and took painstaking research to establish.

The crux of the germ theory of diseases rests on the nature of germs. Microbes, first observed under the microscope by Antony van Leeuwenhoek in 1675, remained a laboratory curiosity for more than a century. No one knew what they did or even where they came from. Controversies about their nature lingered, because experiments with microbes were difficult and slow coming. As late as 1840, when physiologist Jacob Henle hypothesized the causes of contagious diseases to be tiny organisms that invade the body, multiply in it, and die out upon cure, he could not cite any direct empirical evidence.[5]

One issue that any germ-based theory must resolve was whether microbes generate spontaneously from inorganic matter. Most ancient and medieval scholars believed in spontaneous generation, having observed the unbidden appearance of maggots in rotting meat. Many experiments to show that microbes could not appear by themselves in sterile media were inconclusive, frustrated by the difficulty to exclude contaminating microbes, especially from the air. Finally in 1857, Louis Pasteur performed a series of careful experiments that convincingly refuted spontaneous generation. Continuing investigations established microbes to be specific life forms that reproduce only from their own kind.

Pasteur's research was partly motivated by wine brewers who asked him to investigate why their alcoholic fermentation processes sometimes failed. He designed experiments that confirmed previous speculations that fermentation and putrefaction result from the activities of microorganisms. Furthermore, microbes are also responsible for diseases of silk warms. His demonstrations, clear and highly publicized, were widely accepted. Influenced by them, Joseph Lister in 1865 developed antiseptic practices for preventing post-surgical infection. The germ theory began to take shape, although its connection to human diseases was still vague.

Pasteur is usually acknowledged to be the founder of microbiology. His work on spontaneous generation and fermentation, although not directly involved with illness, was essential to the emergence of the germ theory of diseases, for it established the biological nature and causal efficacy of microbes. In 1876, at the age of fifty four, Pasteur turned his resources to diseases of large animals and humans. His first two targets were chicken cholera and anthrax.

Competition in anthrax research

Anthrax nowadays is mainly known as a choice weapon for biological warfare and terrorism. An anthrax attack in the days following September 11, 2001 killed five persons in the United States and terrified a nation already on edge. Actually anthrax in its natural state seldom infects human beings. It is mainly a disease of sheep and cattle that used to wipe out flocks, threatening the livelihood although seldom the life of farmers.

Good news for the farmers came in May 1881, when Pasteur introduced a vaccine in a public experiment using fifty sheep. Half of the sheep were vaccinated, the other half not. Then all fifty were injected with anthrax. The experiment featured in the climax of an Oscar-wining film, in which Pasteur calmly approached the resting sheep in the decisive morning, and all the vaccinated ones stood up to greet him, leaving by their feet twenty five carcasses. The Hollywood construction, however, is less interesting than the real event. Pasteur was so uncertain about the risky experiment he fled and learned of its successful outcome only by telegraph.

Pasteur, prestigious scientist and director of a new laboratory in Paris devoted to contagious diseases, came into competition in anthrax research with two young provincials, the French veterinarian Jean-Joseph Toussaint and the German physician Robert Koch. Toussaint was crushed and would be forgotten if his credits were not revealed by recent research into Pasteur's notebooks. Koch became Pasteur's archrival and fought a credit battle with him.

The secret revealed in Pasteur's notebooks was that the vaccine he used in the famous public experiment was not the one he said it was but one developed by his aid Charles Chamberland with significant input from Toussaint. Toussaint had announced an effective anthrax vaccine as early as July 1880. Pasteur dismissed it as unreliable in a stormy session of the Academy of Medicine in Paris. Competition between the two continued. Pasteur tried to make a vaccine from anthrax bacilli attenuated by exposure to oxygen. Toussaint tried various methods of attenuating anthrax bacilli and settled on chemical treatment. Working alone with little resource, he had difficulty making the process stable. He told Emile Roux in Pasteur's group about his chemical method. Chamberland tried various chemicals to make vaccines. Pasteur chose one of Chamberland's chemically treated vaccines for his 1881 public experiment, because his own oxygen-treated vaccine was not ready. Nevertheless he announced that the vaccine used was made by his own method. Spectacular success of the experiment won Pasteur unprecedented glory and considerable financial benefit. Toussaint disappeared from the scene. In his detailed account of the affair, Pasteur scholar Gerald Geison observed: "his [Pasteur'] conduct vis-à-vis Toussaint was in keeping with his treatment of other competitors who encroached on what he considered his territory."[6]

Pasteur's public demonstration of the anthrax vaccine was a sensational finale of a long research process involving many people. Neither he nor Toussaint was the first to investigate anthrax, although his work on fermentation did inspire the first investigator, Casimir-Joseph Davaine. The stick-shaped anthrax bacilli are giants among microbes. Furthermore, they line up with each other like beads on a chain, making them visible under crude microscopes. People had already observed them in the blood of anthracic sheep in 1863, when Davaine suggested them to be the

cause of the disease. However, Davaine could not back his suggestion experimentally, nor could his germ theory explain why a herd of healthy livestock without any contact with infected animals could suddenly die of anthrax.

Koch solved the mystery in 1876. A small-town doctor and science enthusiast, Koch built himself a laboratory with mostly home-made equipment and jumped on the investigative opportunity when an anthrax epidemic broke out among sheep in his countryside. Like Davaine, he believed that the anthrax bacillus caused the disease. He also believed that to understand it one should start with its biology. Tracking the complete life cycle of anthrax bacilli inside the host and out, he discovered that under adverse conditions, they form heat-resistant spores that lie dormant for a long time, only to germinate, multiply, and wreck havoc when favorable conditions arrive. The stability of the spores explained why anthrax persists in pastures long thought to be cleared and flares up unexpectedly. (It also explains why anthrax is a favorite for biological weaponry; their hardy spores are easy to store and transport as powder in envelops or more dangerously, disperse as aerosol).

Koch realized that the regular presence of anthrax bacilli in anthracic animals demonstrated only a symmetric relationship between bacillus and disease; the bacillus could cause the disease, or the other way around, or the two could just happen to coexist. To prove that the bacillus is the cause, one should demonstrate that it induces disease in healthy animals. He cultured anthrax bacilli derived from sick animals and injected them into experimental mice. As a control, he also used other bacilli, some of which resembled anthrax bacilli, others were present in his culture medium. These other bacilli had no effect on the animals. However, he reported, inoculating of spores "derived from completely pure cultures of *Bacillus anthracis*, and every time the inoculated animals die of anthrax. It follows, therefore, that only a species of Bacillus is able to cause this specific disease."[7]

Koch presented his results to the scientific community. Although he was an "unknown physician from a rural Polish town," his conclusion based on careful experimentation and rigorous reasoning won wide although not universal academic approval.

Pure microbial culture was extremely difficult to attain in those early days when experimental methods were primitive. Some critics argued that Koch's result was inconclusive because he failed to show that his culture of anthrax bacilli was indeed pure. The dispute drew Pasteur into anthrax research. He filtered the bacilli culture, passed the culture through new experimental animals, and showed that the purified culture did cause anthrax. Having silenced the critics, he published a paper in 1877, in which he referred to Koch but argued that only his own method was capable of ensuring the purity the bacilli culture. Therefore, he, Pasteur, was the first to demonstrate the causal agency of the anthrax bacillus.

Pasteur continued to work on anthrax, culminating in the vaccine of 1881. Koch did not; he was in no position to do so. After presenting his result to academia, he returned to his home laboratory and devoted whatever time he could squeeze between medical calls to discovering the bacteria for wound infection. Pasteur had secured the territory he considered his.[8]

In 1880, Koch finally succeeded to quit his country practice for a full-time research job in Berlin. Given adequate resources, he developed novel staining and culturing techniques in one year. The next year he discovered the bacillus that causes tuberculosis, and the next, the bacillus for cholera. Abruptly, a picture readily acknowledged in posterity emerged: At the beginning of microbiology and the germ theory of disease stood not one giant but at least two, Pasteur and Koch.

Both brilliant, industrious, tenacious, and passionate for microbes, the two diverged widely in temperament and style. Pasteur was a chemist by training, imaginative in conception, a dazzling rhetorician with French flamboyance, and inclined toward personal means of disease prevention such as vaccines, which fit well into his need to raise private subscriptions to partially support his laboratory. Twenty one years his junior, Koch was a physician by training, ingenious in experimental design, a plain speaker who persuaded by clear logic and Prussian thoroughness, and inclined toward public sanitary measures for preventing diseases, which fit well in his mainly government funded laboratory. Both patriots in the aftermath of the 1871 Franco-Prussian war that preceded the unification of Germany, they had nationalist antagonism.

For microbiology, the experimental techniques that Koch developed, especially his solid culture, are as important as the bacteria that he discovered. Semi-synthetic media for growing bacteria in laboratory containers instead of animal bodies are essential for microbiology, for they enable microbiologists to pinpoint what they are investigating. They were first introduced by Pasteur in 1860. The early media were all liquids. To obtain pure-line cultures from liquid media were extremely tedious and difficult; things easily mixed up in fluids. Contaminations were easy to get in but hard to detect, results were uncertain. Koch introduced a solid culture in 1881. It consisted of a plate supporting a gelatin-like substance that contained the required nutrient. Pin-sized drops of bacteria inoculated on the surface of the substance grew into tiny colonies well separated from each other, each consisting of only the descendents of the original inoculants. Simple, clean, and reliable, the solid culture technique was revolutionary and is still used today. When Koch presented it in an international congress, he was met and congratulated by Pasteur in person.[9]

If Pasteur, who did not read German, was unaware at the time of their meeting that a short while ago Koch had published his second major paper on anthrax, he soon knew. The case of anthrax is of historical importance because it is the first to establish that a specific germ causes a disease, thus putting not only the germ theory but also the germ theory *of diseases* on firm ground. With the petulance of an upstart who felt cheated of his credit by a don, Koch criticized Pasteur's work, maintained that they added nothing to the etiology of anthrax, and credited Toussaint to be the inventor of the anthrax vaccine. Pasteur responded by criticizing Koch's work and reiterating his own claim to be the first to demonstrate causality. A sometimes vitriolic quarrel ensued, fanned by nationalism and the French-German competition in cholera investigation. However, it was not merely a credit battle; the debate had much technical contents. As Pasteur dismissed Koch's result for the impurity of culture, Koch, with his superior solid culture in hand, in turn dismissed Pasteur's result for the impurity of culture. The debates on culture purity and other methods sharpened the scientific thinking of both and helped subsequent research.[10]

Scientific research is highly competitive, and fighting for credits is a favorite sport of scientists. The Koch-Pasteur dispute was unusual for the strong nationalistic sentiments of both sides, which sometimes leaked into their polemics. Did this seamy side of the research process irremediably contaminate the results of research, so that the anthrax bacillus was not a natural cause of the disease but a social construction? Did personal loathing and national rivalry localize knowledge, so that the germ theory constructed in France was "true" only there and not in Germany or elsewhere?

Koch questioned Pasteur's announced method of making anthrax vaccine. In response, Pasteur arranged to have his vaccine tested in Germany. At first it did not work. The inability for others to readily reproduce the results of an intricate scientific experiment is not uncommon. For instance, some Italian and Austrian scientists were unable to reproduce Pasteur's rabies vaccine. Two opposite interpretations for disagreements in experimental exist. Postmodern sociologists of knowledge maintain that the results should be incommensurate because all "knowledge" is local and inalienable from the culture of its production.[11] One should not expect "knowledge" of anthrax constructed in France to be applicable in Germany. In contrast, scientists demand the disagreements be resolved one way or another, because the reality investigated is objective and should be the same to investigators in various cultures. The first experimentalist may have blundered; or more likely the followers may need more practice in climbing the steep learning curve for complicated experiments. Or different experiments may have unwittingly involved different real-world conditions, then bringing these conditions to light may lead to more discoveries. In short, as opposed to subjective local knowledge, scientists insist on objective knowledge that is capable of accounting for varying local real-world conditions. When the first German test of the anthrax vaccine failed, scientists pointed not to the limitation of the French culture but to an objective condition: the experimental sheep were of a different breed. If they were right, then investigative focus would turn to the sheep and perhaps lead to valuable information about the correlation between breed and immunity. It turned out they somehow bungled their first trial; a second test succeeded. Anthrax vaccine made in France was accepted in Germany, despite nationalism.

Antagonism did have consequences. Pasteur's opposition delayed the adoption of Koch's solid culture in France, and Koch's opposition delayed adoption of Pasteur's rabies vaccine in Germany. Nevertheless, these were temporary aberrations. The French soon adopted solid culture. Koch himself adopted Pasteur's method in organizing an anti-rabies vaccination service for Germany. The objectivity of science triumphed over subjective prejudices.[12]

Good science and bad science in tuberculosis research

Tuberculosis, the white plague, has Janus faces like no other disease. On the one side it is the disease of the impoverished mass, the struggling laborer with sunken chest; on the other it is the disease of the cultural elite, the pale beauty with brilliant eyes. Black death may be more disastrous, blue horror and yellow fever more terrifying, but white plague was unsurpassed in romanticism, in its long list of celebrity victims, and its vivid imageries in poetry, operas, and Victorian literature. Scholars of symbols and values say "it is emphatically a disease of the

nineteenth century." This view of the white plague as a temporally localized disease is a construction of the Western high culture.

Tuberculosis has been endemic in most of Eurasia and perhaps America for millennia. Paleontologists identified genetic remains of the tubercle bacillus in mummies of ancient Egypt and pre-Columbian Peru. Ancient texts described symptoms of fever, blood spitting, and above all slow but inexorable emaciation of the body. From the Greek *phthisis* to the Hindu *xoy* to the Chinese *lao* to the English *consumption*, people in many lands named it by words of similar meaning: wasting, waning, exhausting.[13] A mainly chronic pulmonary disease, it drags on for years, reducing a person to a skeleton before the final blow.

As with individual ailment, tuberculosis epidemics run in slow motion, waxing and waning in centuries. Epidemiological studies find that in Europe and North America, tuberculosis peaked in early nineteenth century. In other parts of the Globe, it is in various phases of its course, depending on when the epidemic commenced. In Japan, for instance, it surged since the 1880s and peaked after 1920. Worldwide in 2000, there were an estimated eight to nine million new cases, eleven percent of which in persons with HIV infection. They occurred mostly in developing countries of Asia and Africa, but incidences were increasing in Eastern Europe. Despite antibiotics, almost two million died annually.[14]

Before mid eighteenth century, people had two explanations for the cause of consumption: heredity and contagion. Proponents of hereditary disease pointed to the observation that consumptive cases often clustered among members of the same family. Proponents of contagious disease countered that the clusters occurred because family members living under the same roof more readily passed the disease around. Sick people would also spread the disease in the community when they went out, and abroad if they traveled. For fear of contagion, some Italian and Spanish cities promulgated laws regulating migration and disposal of diseased bodies in the early eighteenth century. These laws were later repealed, as doubts about causes continued.[15]

Besides the advancement of physiology, two late eighteenth century changes had great impacts on medical knowledge. The first was the transformation of hospitals from waiting rooms for death into facilities for cure. The second was the appearance of clinical laboratories. They enabled physicians to observe a large number of patients, perform systematic autopsies, design experimental tests on tissues and cultures, and delve into causal factors beyond symptoms of individual patients. Anatomical pathologists began to correlate diseases with lesions of internal organs and tissues. Based mainly on postmortem of those died of various consumptive diseases, Gaspard Bayle and René Laënnec announced in 1803 that the corpses shared a common characteristic; they had tubercles in all their organs. This observation led in 1839 to a new name for consumption, tuberculosis.

The contagious nature of tuberculosis was definitively demonstrated in 1865 by army surgeon Jean-Antoine Villemin. He found that the sputum and some glands of tuberculosis patients contained virulent principles that, when inoculated into rabbits and other laboratory animals, induced diseases similar to that of tuberculosis. His results were confirmed in 1882 by Koch, who isolated the culprit microbe, the tubercle bacillus.

Koch's 1882 paper on the tubercle bacillus was hailed by the scientific community as a breakthrough, although it was not the first to identify a bacterium for a human disease. Bacteria associated with pneumonia, gonorrhea, leprosy, and typhoid had already been observed.[16] Tuberculosis was a high profile disease and the tubercle bacillus was especially small, slow growing, and difficult to observe. However, what scientists found most compelling was Koch's ingenious experimental techniques and clear arguments, by which he connected a mass of evidence to demonstrate not only the *existence* of the tubercle bacillus but also its being the *causal agent* of tuberculosis.

The logic behind Koch's arguments that established the tubercle bacillus as the cause of tuberculosis was quickly extracted by others and stated as a general principle. It came to be called *Koch's postulate* and remains influential today: To establish a microbe as the necessary cause of a disease, it is sufficient to demonstrate that:

1. The microbe is present in all organisms suffering from the disease.
2. The microbe can be isolated from organisms and cultured in a pure state in artificial media.
3. Inoculation of the pure culture into healthy but susceptible experimental animals can induce a disease with similar symptoms.
4. The microbe can be recovered from the animals with induced disease.[17]

Koch's postulate accentuates the biological nature of an agent in tracking it through a complex causal network. In a recent review of their extension to molecular microbial genetics, microbiologist Stanley Falkow observed that it is not a dogma but a guideline and working hypothesis. He quoted remarks of his colleagues Fredericks and Relman: "The power of Koch's postulates comes not from their rigid application, but from the spirit of scientific rigor that they foster. The proof of disease causation rests on the concordance of scientific evidence, and Koch's postulates serve as guidelines for collecting this evidence."[18]

With reasoning that would become Koch's postulate, Koch tied together data from 98 cases of human tuberculosis, 43 pure cultures of bacilli, and 496 experimental animals to demonstrate that tubercle bacilli are neither epiphenomena nor products of the disease; they cause tuberculosis. The abundance of data and the logic of interpretation did not satisfy everyone. Critics maintained that inducing disease in animals is insufficient to prove causation in humans. However, submitting to the ethical proscription on human experiments, most scientists thought Koch's demonstration of causation good enough.[19]

Koch claimed to have proved that a patient who has the tuberculosis disease is necessarily infected by tubercle bacilli. However, he did not claim that a person infected by the bacilli necessarily get the disease. In other words, the bacilli are insufficient to cause the disease. Not everyone living in the same infectious environment contracted the disease, and many physicians argued strongly that a person's predisposition was a causal factor, so that the bacillus, even if necessary, is by itself not sufficient for tuberculosis.[20] Well aware of the argument, Koch discussed in length the conditions under which an infected person remained healthy. Furthermore, he explicitly asserted in his papers that he did not address causal conditions in

which bacilli spread to infect people, and he cautioned against rash countermeasures because these actions must reckon with many social factors.[21] His reasoning was clear, rigorous, and conscientious in bringing out limitations. The quality of his argument and supporting evidence impressed the scientific community, not his prestige; in 1882 he just joined the major league.

By 1890, Koch was professor, director of a new institute, and decked with academic and national honors. Medals, however, sometimes can weigh like millstones. The discovery of the tubercle bacillus had not lead to a vaccine or cure – not until the 1920s was the acceptable although controversial vaccine BCG introduced and not until 1943 was the first effective antibiotic streptomycin discovered. Patients and physicians were understandably impatient.

Koch was mainly concerned with the biology of microbes, for which he differed from Pasteur, who was most interested in therapeutic. Nevertheless, for once Koch turned to his secondary interest, an act he would later regret. A cure for such a widespread deadly disease would be sensational and would bring national glory. Pressure from government officials was high. In August 1890, Koch mentioned in a medical congress that he had preliminary results of a substance that halted the growth of tubercle bacilli in laboratory cultures and guinea pigs, adding that he had made no trial on humans. Now he added popular pressure on himself. In November he published "A further communication on a cure for tuberculosis." Before reporting favorable results on limited human trials, he wrote: "It was originally my intention to complete the research, and especially to gain sufficient experience regarding the application of the remedy in practice, and its production on a large scale before publishing anything on the subject; but in spite of all precautions, so many accounts have reached the public, and in such an exaggerated and distorted form, that it seems imperative, in order to prevent false impression, to give at once a review of the position of the subject at the present stage of the inquiry."[22]

Tuberculin was the name of Koch's remedy. The process of its preparation was not published until early January of 1891. In the November 1890 paper, Koch withheld the information "as my research is not yet concluded." There he reported that humans were far more sensitive to tuberculin than guinea pigs. A low dosage invariably induced reactions in tuberculosis patients but not in healthy people, upon which he predicted that tuberculin would form an indispensable aid to diagnose doubtful cases of tuberculosis. Therapeutic effects were less apparent. In patients whose tuberculosis affected their skin, tissues of skin lesion were observed to die and fall off within two or three weeks after injections of tuberculin. With these data, Koch concluded: "the remedy does not kill the tubercle bacilli but the tuberculous tissue, and this gives us clearly and definitely the limit that bounds the action of the remedy."[23]

"Miracle cure!" Clattered telegraph lines in all directions. Thousands of patients, some on their last breaths, swarmed Berlin. Frightened Berliners scrambled, not to erect a wall, but to pour disinfectant in all public spaces. The scientific community was as skeptical as enthusiastic. Among the more than a thousand physicians who came to Berlin was Conan Doyle. With the logic of a Sherlock Holmes, Doyle reasoned that removing infected tissues could result in a complete cure only in very exceptional cases, because the bacilli survived and affected many organs of the body: "Your remedy does not treat the real seat of the evil. It continually removes the traces of the enemy, but it still leaves him deep in the invaded country."[24]

Doyle's view was shared by some of Koch's German colleagues. Skepticism mounted as results of administering tuberculin accumulated. By mid 1890, more than two thousand patients received tuberculin injections. An extensive study found improvement in less than twenty percent of those treated. The only exception was for a mild form of tuberculosis that affected only the skin; here it helped almost ninety percent sufferers. These data were difficult to analyze for therapeutic effects, because they were not compared to those from controlled groups who did not receive treatment. Furthermore, tuberculin also turned out to be two-edge sword. One the positive side, it proves to be a simple and effective diagnostic tool for tubercle infection, an improved version of which is still widely used today. We now know that it works in diagnostic tests by inciting allergic reactions from people infected with tubercle bacilli. Unfortunately in the early days when even the notion of allergy was unknown, injections of therapeutic dosages sometimes led to violent allergic reactions or even deaths. Tuberculin as a cure was quickly discredited in Europe and Canada, although it retained some popularity in the United States for decades.[25]

Fiascos such the tuberculin "cure" do occur in scientific research. Scientists call them *bad science* and reject them on objective grounds. The distinction between good and bad sciences is rejected by postmodernists, who maintain that all scientific results are equally constructed, and they are not equally accepted only because the proponents of some are more powerful than proponents of others. This postmodern doctrine is refuted by the two episodes of Koch's involvement in tuberculosis research. Koch was an upstart in 1882 when he discovered the tubercle bacillus, but his discovery was accepted, based on its solid data and convincing argument. He was a world-class authority in 1890 when he announced the tuberculin "cure," but his power did not make his science good and acceptable; it was received with skepticism because of the scarcity of data and the weakness of his reasoning linking the data to the therapeutic claim. Both cases excited much debate that clarified doubts, and the acceptance or rejection was reinforced by subsequent data. Science is not a mere power play.

Some sociologists write disparagingly of the "secrecy" under which Koch discovered the tubercle bacilli. To be cautious about divulging results prematurely does not necessarily violate the openness of science. Discovery of a complex phenomenon is a much more difficult and intricate process than arbitrary construction. Luc Montagnier, who discovered the HIV virus, warned people not to be "mistaken to think that all laboratory research necessarily leads to publications of varying degrees of importance and fame. In fact, 90 percent of all experiments lead to nothing whatsoever; most of the time some unforeseen technical snag arises, or the initial idea proves faulty. The day-to-day life of researchers consists mostly of disappointments, with the occasional success that allows them to maintain their enthusiasm."[26] Because blunders and blind alleys are so common in the process of discovery, conscientious researchers tend to rein in their enthusiasm and keep quiet while they double check and critically test their results. Such good scientific practice was violated by Koch in his handling of tuberculin. Perhaps if he had worked "secretly" to complete his research before announcing anything, he would have judged objectively that tuberculin made a good diagnostic tool but not a vaccine or a cure. In that case he would have made a good scientific discovery that would improve tuberculosis care and enhance his own reputation. As it happened, however, his premature "openness" produced only bad science, brought disgrace to himself and above all harm to patients cheated by false hopes if not treated by an untested drug.

Koch's tuberculin debacle is similar to a case a hundred years later, when pressure to dispense untested AIDS treatment led to similarly undesirable outcomes. These cases illustrate the danger of doctrines that mix up objective scientific judgments with political pressure and social hype.

The science and politics of cholera

Some may think tuberculosis romantic, but no one can so regard cholera. Acute diarrhea and vomiting, leaden-blue complexion and painful convulsion caused by fatal dehydration are so ghostly cholera is called the dog's death and blue horror. As quick as the white plague is slow, cholera often kills in a day. Although tuberculosis killed many more people, it was the fear of cholera that pushed governments to institute boards of health and improve public sanitation.

Cholera is endemic in South Asia, especially in the Ganges delta region. It broke out of the Indian subcontinent in 1817 and produced six pandemics in the nineteenth century. Like a forest fire, a cholera pandemic pushed along a rough direction and sparked blazes sporadically in its way. A pandemic could last a long time as it swept across the Globe, but the epidemic it sparked at each locality usually flared up and declined rather quickly.

The first cholera pandemic spread eastward to China and Japan and westward to reach Russia and the Middle East. The second, started in 1829, reached Moscow the following autumn, hit Western Europe in 1832 and quickly jumped the Atlantic to America, where it continued westward to the Pacific. It lasted for decades, revisited Europe and America in the late 1840s, and shaded into the third pandemic of the early 1850s. The fourth pandemic of the early 1860s was followed by two decades of reprieve. The fifth and sixth pandemic spared most of Europe and America. In all six pandemics the disease retreated, putting down no root except in its endemic home. This changed in the pandemic that proceeded in the decades following 1961. This time cholera took root in many places that it invaded, especially in Africa and Asia, and multiple drug-resistant strains emerged. Another new resistant strand appeared in 1992. The cholera years are not mere history.[27]

When cholera arrived in Europe, its horror rekindled debates about the nature and causes of diseases. Epidemics were not new, and people believed that diseases that struck erratically and killed massively were not without causes. Some ancients attributed causes to the gods, as in the Homeric story of Apollo shooting pestilence at Greek warriors or the Biblical story of Yahweh throwing a plague on Egyptian civilians. Others found them in the cosmos; the name "influenza" originated from the medieval belief that the stars influenced diseases. More enduring are social constructions of diseases as punishments for "immorality." Syphilis in the nineteenth century and AIDS in the twentieth are favorite subjects of such constructions. In a similar vein, cholera was constructed to be a scourge on the filth and depravity of the poor. The more productive trend, however, is to seek natural causes.

Two major conjectures about natural causes of diseases existed since at least the Renaissance. In one, diseases were caused by *miasma* or bad air arising from organic decay, filth, or other conditions of the local environment. The other held that diseases were *contagious*; infectious

principles pass from patient to patient, through direct contact, physical items, or at a distance.[28] Both conjectures had some empirical support, and some scientific studies were attempted to decide between them. For instance, the French in 1822 carried out careful investigations on yellow fever and demonstrated that people with no possibility of contact got the disease. This result was subsequently confirmed by American scientists. These early researchers could not be blamed for overlooking mosquitoes; no one at the time suspected the possible role of insect vectors.[29] John Snow's epidemiological study during the 1853 cholera outbreak in London demonstrated that the disease spread through contaminated water. However, it left open the nature and origin of the contaminants, which could be environmental products or contagious agents. Data were sparse, but they seemed to tilt against the contagious nature of diseases until the 1870s, when the tide was turned by the germ theory.

The notions of miasma and contagion were vague. They were not mutually exclusive if examined in details. Miasma could abet the spread of contagion. Conversely, contagious agents in patients' excrements and spits could add to miasma. However, the two conjectures clashed in one aspect that had great political consequences, which kept the debate polarized. Miasma was local, contagion mobile. If diseases traveled with patients, then visitors and immigrants may bring them into a community, a danger the host community need not worry about if diseases stuck to local conditions. How the community should act depended on what people believed about the nature of the disease.

Fearful of importing diseases, many Mediterranean ports instituted quarantine since the fifteenth century. The measure gave some protection for inhabitants of the ports. However, ships and their cargos and sick crews sitting in quarantine cut into the profits of the owners of ships and cargos. Many who wanted to get rid of quarantine declared it useless because diseases were local to the ports and did not come on ships. Governments quarreled. Partisans promoted one or the other explanation of diseases that fit their financial and political interests. Rivalry was further fanned by rising imperialism in the late nineteenth century.[30]

Cholera struck Egypt in 1883. In three months, it killed some 50,000 inhabitants of Cairo and Alexandria and threatened to spread to Europe. This was the first outbreak since the Suez Canal opened and the first since the germ theory of disease gained scientific credence. What caused cholera? Could the increased traffic through the canal more readily brought disease-causing germs from India? Britain, France, and Germany each dispatched a team to investigate.

Britain, the world's dominant shipping and imperial power, had just become the effective suzerain of Egypt. Despite Snow's epidemiological work, the British government maintained that cholera was caused by local conditions and was preventable not by quarantine but by sanitarian inspections. For a decade it had worked hard to dismantle the Mediterranean quarantine system, specifically to ensure unrestricted passage through the Suez Canal to India, its greatest dependency soon to become its colony. When the cholera struck, it was under international criticism for risking Egyptian lives for British profit. To deflect the criticism, the British government commissioned an investigation. It rejected the petition of an officer who was a microbiologist and scientific authority in cholera. Instead, it picked William Hunter, a physician with a sanitarian stance. Hunter's team, which lacked microbiologists and experts in microscopy, quickly concluded that cholera was not imported. The outbreak was locally caused

by unclean eating habits of the Egyptian poor and above all by an unusual weather condition that reactivated the poison left from the previous outbreak. Hunter was knighted.

The French delegate headed by Roux of the Pasteur Institute and the German delegate headed by Koch arrived in Alexandria about a month after the British commission. Both were keen microbe hunters. However, the epidemic had already peaked when they arrived and they had difficulty finding enough corpses for dissection and microbial culture. The French team lost a member to cholera and returned home saddened.

Koch's team found comma-shaped bacilli in the small intestines of cholera victims. They were not the first to see them. The bacillus had been described by Filippo Pacini in 1854, just a year after Snow demonstrated the water-borne nature of cholera. Pacini also speculated that the bacillus caused cholera, but he did not prove it empirically.[31] Koch was determined to establish causality just as he did with tuberculosis. His results being inconclusive and the epidemic ending in Egypt, he decided to chase the disease to its home. The team set sail for Calcutta. There they found comma bacilli in the intestines of all forty carcasses of cholera victims they examined. And the bacilli were present only in cholera victims, being absent in all other bodies, including those died of non-choleric diarrhea and intestinal disorder. They isolated and cultured the bacilli. However, they were unable to infect any experimental animal with it. Then they turned to epidemiology. A point epidemic broke out in a nearby village killing seventeen villagers. The team rushed to investigate and succeeded to find comma bacilli in the village's communal water tank. Koch argued this may served as a natural experiment indicating that the bacilli in the water caused the villagers to get cholera. Together with the constant and exclusive presence of comma bacilli in cholera victims, this led him to conclude that the bacilli caused cholera. When they returned to Europe in 1884, cholera broke out in southern France. Koch went there and identified the comma bacillus he isolated in France with that in Egypt and India.[32]

Koch's assertion that the comma bacillus caused cholera would be fully confirmed by later scientific research. Even before that, it won much immediate support. For instance, the British scientific journal *Nature* reported Koch's result with favorable editorial comments. However, his failure to infect experimental animals with comma bacilli made his case much weaker than that for tuberculosis. Many, including some of his countrymen, remained doubtful. Lively debates ensued, scientific and political.

Reports for the existence of disease-causing germs, which implied that cholera could travel with ships, increased the political resistance to abolish quarantine through the Suez Canal. Britain and British India, which championed abolition, found themselves alone in the 1885 International Sanitary Conference. They knew what to blame. One British official called Koch's assertion "dangerous and unverifiable." He wrote: "I am also very anxious to avert the evil consequences that may accrue from the effects of this so-called discovery on our sea traffic."[33]

Hunter's report that weather caused the Egyptian cholera epidemic was no longer effective in bolstering British policy. The British government decided to send a reputed microbiologist who could stand up to Koch. Screening out sympathizers of the germ theory of disease, they chose Emanuel Klein. Promised that they would be "perfectly untrammeled in their method of inquiry," Klein's team went to Calcutta and Bombay. They performed similar experiments and

observations as Koch did, obtained similar results, but drew the opposite conclusion. The data did not warrant that comma bacilli caused cholera; their presence in victims was an epiphenomenon.

The British government convened a committee to review Klein's report. The committee, whose members included Queen's physicians and eminent scientists, published in 1886 a paper entitled "The official refutation of Dr. Robert Koch's theory."

Did Koch invent a "cholera bug" for his personal glory? Did Klein construct "data" to suit national interest? Alternatively, was their disagreement mostly objective, based on genuine insufficiency and ambiguity in the available information?

We are mainly concerned not with how colonial officials use science for political ends but with the judgments of scientific communities. Klein's was a scientific report, and its merits against Koch's theory were extensively debated among British scientists even before the government committee convened. Whatever motivated the committee, its "Official refutation" advanced not political but scientific reasons. Despite its political weight, the "Official refutation" was published in an obscure journal. The more prestigious scientific and medical journals *Nature*, *Lancet*, and *British Medical Journal* did not toe the official line. The *British Medical Journal* published lengthy articles by both Klein and his opponents. The *Lancet* published digests.

Klein and the official committee directed their criticism at the two weak spots of Koch's theory: the failure to infect experimental animals and the failure of some people who ingested comma bacilli to get cholera. These were objective points pertaining to the real-world topic under consideration, not the subjective motivations of their authors. The political bias of the authors may have prompted them to emphasize these points, but others with no political axe to grind raised similar criticism. It is wrong to interpret the skepticism as mere politics. Quite the contrary, scientific objectivity would be lost if they were not debated and cleared up by further research. If they were, Koch's theory would become a dogma accepted blindly.

Infecting experimental animals with a bacillus is a part of Koch's postulate for a sufficient proof of the bacillus being a necessary cause of a disease. But that particular proof itself is not necessary; a causal factor can usually be demonstrated in several ways. Koch answered his critics. Two explanations were possible for the failure to infect experimental animals, either the comma bacillus did not cause cholera, or it did but only in humans. The issue could be resolved by human experiments, but that were prohibited. Was it plausible that a bacillus infected only humans? Koch answered yes; leprosy and typhoid fever, the commonly acknowledged infectious diseases, too could not be communicated to animals. Thus he argued that the regular presence of comma bacilli in cholera victims, and in no one else, should be good enough to demonstrate causality. However, this argument by analogy was not strong. As Kline contented, constant and exclusive presence of bacilli in cholera victims could equally indicate that the bacillus was not the cause but an effect of the disease, or an epiphenomenon that had nothing to do with it.

Epidemiological observations too were inconclusive. Koch observed that some villagers who drank contaminated water got cholera. Klein observed that many who drank contaminated water

did not get cholera, nor did most family members of victims who were easily exposed to the choleric discharges. We now know that the comma bacillus is a necessary but not sufficient cause for cholera. The great majority of infected people either develop no symptom or at most a mild diarrhea. According to dosage of bacilli, resistance of the population, and other factors, only between one percent to thirty percent of those infected with comma bacilli develop cholera.[34] Klein did not construct "data." Upon the meager evidence available at that time, he could objectively deny the causal efficacy of comma bacilli. The editorial board of *Lancet* expressed it best when it urged readers not to discard Koch's theory rashly based on Klein's report: "The value of the work of the English Commission may then appear to lie in its having done much to clear the way for further research which it would be worse than folly now to neglect."[35]

Research proceeded. Skeptics of Koch's theory made bold demonstrations. The German hygienist Max Pettenkofer publicly gulped down a tube of bacilli. He did not know it, but his odds in the game were similar to that of Russian roulette. Not all who played were as lucky as he was. Elie Metchnikoff, a renowned immunologist working in France, was also lucky when he swallowed bacilli himself. Then he noticed that none of the people living near a contaminated river got cholera and persuaded several townsfolk to ingest some bacilli. They all fell sick and one died. Metchnikoff quickly became a convert to Koch's theory.[36] Gradually, as better epidemiological data accumulated, as knowledge on microbial biology, human immunity, and microbe-host interactions increased, scientific consensus developed that the comma bacillus is a necessary cause of cholera. Politics that may have motivated earlier research find no place in the consensual scientific result.

"Contagion implies quarantine; miasma implies sanitation." Such slogans were common in times when the notions of contagion and miasma were so vague they could mean almost anything or nothing, as exemplified in the remark of a British sanitary official: "All smell is disease." When science gradually shed light on the microbial mechanisms underlying infectious diseases, people began to realize that contagion and bad air were not mutually exclusive but could be causally related. For instance, Koch explained that tubercle bacilli could live for more than a hundred days; therefore, bacilli in sputum dried on streets, ground up into dust by traffic, and carried by the wind could be more effective in spreading tuberculosis than droplets directly expelled by a coughing patient.[37] Such scientific knowledge was invaluable in designing sanitary measures for preventing tuberculosis, such as discourage spitting on streets and cleaning up sputum.

Neither quarantinism nor sanitationism was a single policy. Each encompassed many varieties, and only ideologues deemed them necessarily incompatible. To avoid diseases, peoples and governments over the centuries had tried all kinds of measures and learned from their results. Britain was not merely greedy when it opposed quarantine. It had some objective evidence that quarantine was not always effective. For example, it did not work for yellow fever, the viruses for which are carried by mosquitoes. Cholera, too, easily jumped quarantine; before its cause was known, one had no reason to attempt the difficult task of preventing contaminated waters to leak from a ship. However, the possibility to do some things without scientific knowledge does not imply the superfluity of science. Know-how is vague, and many intuitive measures are like hunting with a shot gun, with low kill rates and high collateral damages. Scientific knowledge

changes the shot gun into a precision rifle. Testing waters for the comma bacillus, for examples, would be an effective sanitary measure for cholera prevention. Ironically, Britain's case against quarantine could be helped, not hampered, by the germ theory of disease. Koch used to support quarantine, but convinced by knowledge about comma bacilli that quarantine was ineffective, he abandoned it in favor of water filtration for cholera prevention.[38]

Knowledge that germs carry infectious diseases does not dictate any policy. There are many ways to modify nature to achieve a goal, and there are many goals. Action involves many factors besides scientific knowledge, not the least the willingness to act and the means available. The devil is always in the details, physical details such as disease etiology and local environment, social details such as economic feasibility and political organization. Nevertheless, the complexity of policy does not imply that all things, including the science about physical causality, are fully negotiable constructions.

Notes

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    Various methods exist to test whether a person without symptoms is infected. One, tuberculin, was accidentally invented by Koch, who aimed for a cure. Judged by the results when he tried tuberculin on himself, he probably got tubercle bacilli in him. See R. Koch Koch. A further communication on a cure for tuberculosis (1890). Reprinted in Rosenkrantz, *Consumption*, pp. 356-364.
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22. Koch, Further communication. Koch's words was *Heitmittel*, which was translated as *cure* or *remedy*.
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35. Quoted in Ogawa, Bedfellow.
36. Waller (2002: 153).
37. Koch, Tuberculosis (1884).
38. Baldwin, *Contagion*, ch. 6.