On Darwin, Snow, and Deadly Diseases

An evolutionary approach to disease control could vastly improve public health

by Paul W. Ewald

The other passengers on the London train must have dismissed me as another mental casualty of twentieth-century urban life. I had looked out of the train window, let out a "Ha!" and then chuckled, nodding my head as though I had just been told a joke by an invisible friend. But I didn't care. I had just made a connection between disciplines that was symbolized by what I saw through the window.

The day began like most that summer of 1984. I entered the library of the London School of Hygiene at opening time, holding a plastic shopping bag filled with about a thousand note-covered index cards. Surviving a probing glance from the front desk, I scaled a flight of stairs and hustled to a secluded table sandwiched between floor-to-ceiling shelves of old medical journals. I removed half of my cards and a thermos of coffee that I had hidden in the bag, leaving a hand-width passageway to a cache of cookies, which would fuel me until the library closed. I concealed the cup with the bag and stowed the thermos below the table, out of the librarian's line of sight, to avoid the wrath I incurred when my operations were less clandestine. I then set to work.

I was trying to find out why some diseases are so dangerous and others merely annoyances. My interest had been sparked several years earlier when I read *Man Adapting,* by bacteriologist René Dubos. I was surprised by his statement, "Given enough time a state of peaceful coexistence eventually becomes established between any host and parasite."

I saw no reason why natural selection would always lead to peaceful coexistence, although it might do so in certain circumstances. Consider a population of viruses living within a human host. What if one variant in this population is more adept at exploiting the host's body? Replicating more rapidly, it would win the evolutionary race with its viral competitors and become the predominant variant in the population. It would also make the host sicker and more contagious.

But if the long-term survival of such a virus depends upon its being transmitted directly from host to host, as is the case with the virus that causes the common cold, then the rapid reproducer may pay a high price for its virulence. If the illness is severe enough to immobilize the host, contact with new hosts will be drastically reduced. A more slowly reproducing, milder virus—perpetually being transported by a mobile host to new contacts—would be more likely to prosper.

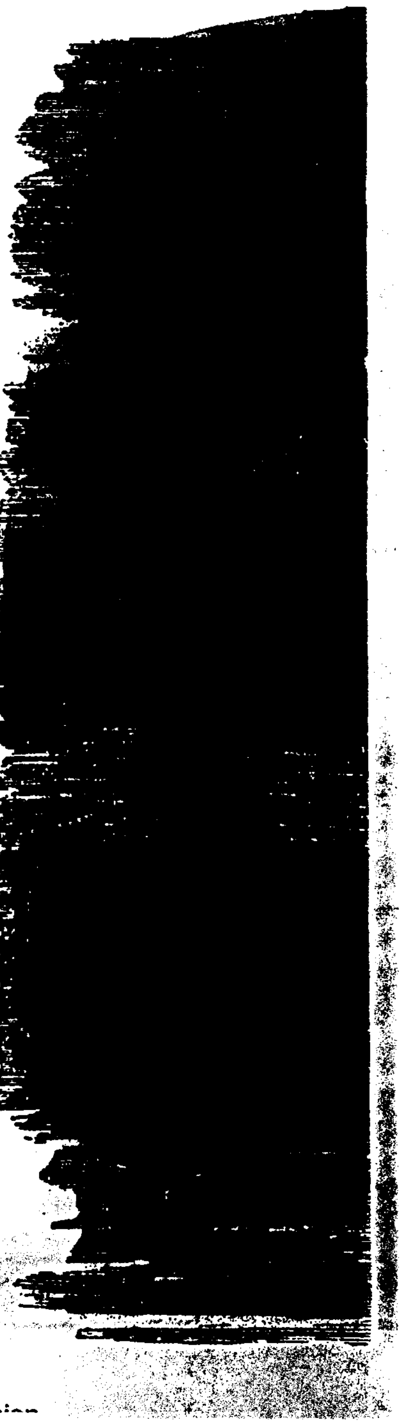
If host–pathogen relations always followed this scenario, Dubos's generalization would be reasonable; viruses would evolve toward a relatively mild state of coexistence with their hosts.

But, I reasoned, what if the pathogen could be transmitted even when the host was immobilized? Then the more rapidly replicating, abusive organism might get the competitive advantages of high reproduction at a bargain price. This seemed to be the case with *Plasmodium falciparum,* a pathogen that causes malaria. Even when its host is immobilized, this protozoan is still easily transmitted to other people by mosquitoes. Generalizing from this argument, I predicted that disease organisms transmitted by biting arthropod vectors should be more severe than those transmitted directly from person to person. I searched the epidemiological literature and found that the prediction passed the test. Vector-borne pathogens like *P. falciparum* and the yellow fever virus are significantly more severe than such host-borne viruses as the common cold.

Evolution may involve long spans of time, but it can be rapid if generations are short and the culling of competitors is intense. Use of antibiotics, for example, can cause staphylococcus bacteria in hospitals to evolve high levels of resistance within a few weeks. If our technology can accelerate the evolution of a bacterium, couldn't other human activities also cause pathogens to evolve rapidly? My attention was drawn to diarrhea.

Each year millions of people die from diarrheal diseases, but the organisms that cause diarrhea are not equally culpable. Some cause deadly diseases like cholera, typhoid fever, and dysentery, but others rarely kill. Are the classic killers maladapted organisms that will eventually evolve toward peaceful coexistence, or are they severe because our activities have made them severe?

This was the question that brought me to the London School of Hygiene. On that summer day, punctuated by surreptitious



An 1858 Punch *cartoon depicted pollution on the Thames. The skeleton is facing the residential area where John Snow completed his classic study of cholera-laden water supplies.*
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sipping of coffee and covert crunching of cookies, I was reading John Snow's book *On the Mode of Communication of Cholera*. Snow was a dedicated, lonely workaholic who spent many years during the mid-nineteenth century trying to understand how cholera was transmitted. He focused on a middle-class residential area of south-central London; the northbound Thames bends sharply to the east and then arcs to the south around the area. Cholera battered the residents in 1849. Snow was looking for risk factors: activities or environmental exposures that could explain why cholera attacked some people and not others. His initial observations made him suspect the water. In one severely affected area he found that

slops of dirty water, poured down by the inhabitants into a channel in front of the houses, got into the well from which they obtained water.... Owing to something being out of order, the water had for some time occasionally burst out at the top of the well, and overflowed into the gutter or channel, afterwards flowing back again mixed with the impurities; and crevices were left in the ground or pavement, allowing part of the contents of the gutter to flow at all times into the well; and when it was afterwards emptied, a large quantity of black and highly offensive deposit was found...evacuations [from cholera cases] were passed into the beds,...the water in which the foul linen was washed would inevitably be emptied into the channel.

Water in this area was supplied by the Lambeth Company or the Southwark and Vauxhall Company. When one of Snow's colleagues examined the water, he "found in it the hairs of animals and numerous substances which had passed through the alimentary canal." He concluded that the water from these companies "is by far the worst of all those who take their supplies from the Thames."

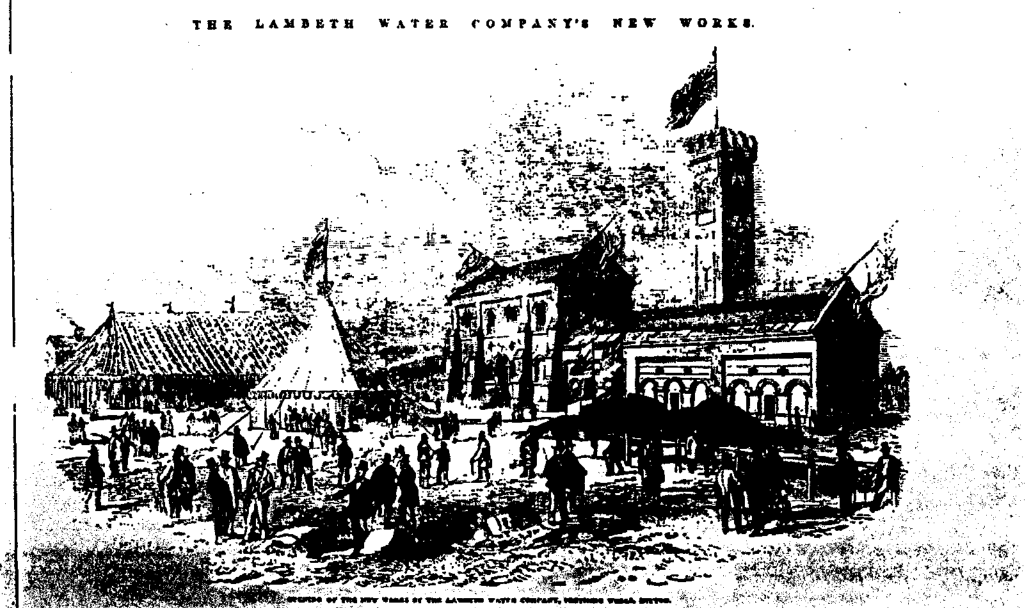
Before the cholera epidemic of 1853, the Lambeth Company moved its water intake to a purer source. Snow realized that a vast experiment had been set before him. Scattered among the houses receiving contaminated water from the Southwark and Vauxhall Company were houses receiving purer water from the Lambeth Company. If water transmitted cholera, the residents served by the Southwark and

Vauxhall Company should have suffered from cholera more than residents served by the Lambeth Company. They did. Snow found that the risk of cholera among Southwark and Vauxhall customers was nearly ten times greater in 1853, even though it had not been greater in 1849, when both companies delivered contaminated water. By showing that cholera could be waterborne, John Snow had established the field of epidemiology.

From an evolutionary perspective, the transfer of the "foul linen," the movement of contaminated sewage into water supplies, and the delivery of contaminated drinking water acted like a horde of mosquitoes transmitting pathogens from immobilized patients. Might such waterborne transmission be responsible for the great variability in harmfulness found among diarrheal pathogens? A quick look at the literature cannot resolve this question because most diarrheal organisms can sometimes be transmitted by water and sometimes not. My task, therefore, was to determine from the literature whether severe organisms tended to be waterborne more often than were milder organisms.

By the time I looked out of the train window, I was a few years into this task. A pattern was taking shape: the lethality of the various diarrheal bacteria correlated almost perfectly with their tendencies to be waterborne. The correlation explained why cholera, typhoid fever, and some kinds of dysentery were so severe. It also suggested a new dimension for disease control. If waterborne transmission favors the evolution of increased harmfulness, then water purification should do the opposite—transform severe pathogens into milder ones. Indeed, records indicate that this transition has happened. Policy makers, however, have recently diverted investments from clean-water programs because field studies did not show a large reduction in frequencies of infection. But frequencies are only part of the story, the epidemiological part, the part that Snow was investigating. The severity per infection is the other important part, the evolutionary part. If the next generation of precise tests shows that water purification transforms severe organisms into mild ones, then we will have a powerful evolutionary tool for taming diarrheal disease.

These ideas forge a link between epidemiology and evolutionary biology, between John Snow and Charles Darwin. Although Snow and Darwin were long dead, I felt as though I had been meeting with them—their printed words had launched their insights through the intervening century. When I looked out of the train window I was aloft with these thoughts, but just as I was coming back to earth, I left it again when I saw a sign at the train station: Vauxhall! Until then the places in Snow's book had just been markers for keeping track of disease outbreaks. But at that moment I realized that I was having both an intercentury tutorial from Snow and a tour



London's Lambeth Company opened a new waterworks in 1852. Its customers therefore received relatively pure water and largely escaped a cholera epidemic that ravaged the city the following year.
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of the places that he had methodically canvassed to establish the field of epidemiology. I later realized that I had begun this tour by walking out of the library.

Snow moved to London in 1836; Darwin in 1837. In the early 1840s Darwin was living on Gower Street, a block north of where the London School of Hygiene would be built. He was, in his words, "collecting facts bearing on the origin of species." At that time John Snow was working on his degree at the University of London, which was across the street from Darwin's apartment. But Darwin and Snow apparently never met and may not have even been aware of each other's earth-shaking contributions. Although Snow was four years younger than Darwin, he died of a stroke in 1858, at the age of forty-five, one year before the publication of *Origin of Species*. Each time I went to the library that summer, I walked down Gower Street, where Snow and Darwin must have walked separately many times during the early 1840s. Chance had put me in the same place, and the printed words in the library had removed the barrier of time, allowing a linkage between Snow's epidemiology and Darwin's evolution.

Isaac Newton paid homage to scientists such as Galileo and Copernicus by writing, "If I see farther than other people, it is because I stand on the shoulders of giants." The rest of us also have the chance to see farther if we do a little giant climbing. As for me, I was teetering with one foot on Charles Darwin's shoulder and the other on John Snow's. We cannot predict precisely what new views will come from the merging of epidemiology and evolution, but we can see many possibilities. A better understanding of the evolution of virulence should allow us to identify interventions that will not only reduce the spread of infections but also force pathogens to evolve to milder states by making harmfulness too costly for them. Diarrheal pathogens may be forced into a benign state by water purification. Vector-borne pathogens may be similarly transformed by the installation of mosquito-proof housing that prohibits transmission from severely ill people. I expect that scientists at the end of the twenty-first century will find it curious that today's health scientists were so skilled at recognizing the importance of molecular biology and biochemistry, but that it took more than a century after the birth of evolutionary biology, epidemiology, and microbiology for us to realize the importance of using evolution as a tool for controlling disease.