Virchow Revisited: Emerging Zoonoses

Virchow’s still-relevant call to consider “one medicine” demands an interdisciplinary understanding of diseases and microbial ecology

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The German physician Rudolf Virchow (1821–1905) was studying *Trichinella* in 1855 when he coined the term “zoonosis.” His work on this disease helped to convince him of the importance of linking human and veterinary medicine, something he emphasized throughout his career. Although Virchow is more widely heralded for his cell theory of disease, perhaps his concept of one medicine will become his important legacy.

Today, our renewed emphasis on disease emergence is blurring the interface between animal and human health, with diseases blending like figures in an Escher drawing. Emerging diseases, a field of biomedicine that began with the discovery of AIDS, continues to expand. Most emerging diseases in humans are zoonotic in origin. AIDS, for example, apparently transferred to humans from primates—specifically, chimpanzees and sooty mangabeys.

Virchow could hardly have envisioned how his concept of one medicine would become so central to public health by the third millennium. In the century and a half since Virchow first used the term zoonosis, we have made incredible progress in the biological sciences, including sequencing the human genome and those of many important microbial pathogens. Ironically, while developing an ever-more-sophisticated understanding of the host, its many responses to infectious agents, and their virulence factors, we also are facing a dramatic increase in the number of new diseases affecting that host, with the majority of those diseases originating in animals.

Several factors help to explain this recent increase in new diseases. First and foremost, the human population continues to expand. Despite current concern over dwindling resources and increasing anxiety about the environment, the human population continues to grow rapidly. Near the end of Virchow’s career, global population was a mere 1.5 billion. Since, then it has grown to 6.2 billion, and is expected to reach 10 billion by 2050. The Malthusian predictions of economic ruin from population outpacing resources proved false throughout the 19th century because technological advances forestalled mass starvation. However, increased numbers of people, extensive travel and trade, habitat changes, pollution, and burgeoning food animal populations encourage the emergence of new diseases—adding up to apocalyptic possibilities, albeit ones that differ from those predicted by Thomas Malthus.

Global trade and travel contribute significantly to the emergence of new zoonoses. For instance, infectious agents harbored within mosquitoes or animals can travel halfway around the world in less than 24 hours, sometimes causing new disease outbreaks. Whereas in the 19th century it took weeks or months for diseases to journey from one continent to another, today they can be transported to the farthest lands in less time than most disease incubation periods. In addition, globalization of technology, information, and finance is creating market forces that drive...
the interconnectedness of industries, cultures, and organisms.

As informed consumers view investment opportunities on their computer screens and act accordingly, the world is no longer defined so much by geopolitical boundaries as by the terms fast or slow. In the fast world, the “electronic herd” generates a volume of international commerce that was inconceivable just a few decades ago. The traffic of people, animals, and animal products continues to grow. World trade tripled in the last 20 years, and tourism is the fastest-growing sector of the global economy, with one in four citizens of the developed world visiting a foreign country each year.

Emerging Diseases Elicit Coping Responses, Questions

With this flux of people and animals, diseases also move at a rapid pace. For example, West Nile virus probably entered the Western hemisphere via a stowaway mosquito or viremic animal in a rapidly moving vehicle—a plane or ship. Once transported across the ocean, that stowaway sparked an outbreak in the eastern United States that catalyzed the integration of public health, the veterinary profession, and wildlife agencies as no other agent of any sort ever had. The presence of a deadly disease in horses, crows, people, and many other species generated an integrated surveillance system that would have met with Virchow’s hearty approval, although he may have grimaced over the protracted maneuvering needed to convince all parties to speak a common language.

Globalization of trade also brought Aedes albopictus, an important vector of West Nile virus, to this hemisphere. This mosquito was not found in North America prior to 1985, when it arrived in Houston, Tex., in a shipment of used tires from Japan. Since then, it has spread to numerous states and has proved very capable of surviving and replicating in container habitats in the peri-domestic environment. There is little doubt that this winged Asian intruder, which is now ensconced in multiple states, will become a major player in many other vectorborne zoonotic diseases.

Questions arise—how or why did the United States import used tires from Japan? The answer comes from reviewing global trade patterns and practices. Houston is a world center for recycling rubber, which is considered more valuable in the United States than in Japan. So, investors did what trade globalization enables: they went on the world market to import a commodity in hopes of generating a profit. The dual truths of globalization and international trade are that it is very lucrative for the players but also seemingly chaotic.

A Quartet or More of Emergent Viruses

As human numbers continue to increase, population contingents enter into different environments that they then modify—giving rise to another major factor in the emergence of zoonotic diseases. For example, several viral agents, living in seeming quiescent isolation in one animal species, have emerged as a result of such changing environments, making spectacular moves into humans to generate florid disease and public health consternation around the globe.

Although Virchow never heard of the Ebola virus, it has made headlines several times over the past decade due to a series of small outbreaks within central Africa. In terms of numbers killed, Ebola is a bit player in the global infectious disease script, particularly when compared with major killers such as tuberculosis and malaria. However, it is now popularized in best-selling books, documentaries, and Hollywood films, making Ebola virus an emblem for emerging zoonotic disease. Another factor that keeps the Ebola story prominent is the ongoing hunt for its animal reservoir. The absence of a definitive host highlights why wild viruses are so humbling. It forces us to recognize that our understanding of the world is so fragmented.

Our poor knowledge of the microflora of animals hit hard in Australia and Southeast Asia when four viruses from fruit bats emerged in recent years to cause both animal and human health disorders. Hendra virus was the first to appear and be recognized. Responsible for a significant outbreak in horses at two different facilities, what made this new virus so noteworthy is that it killed two humans as well. A methodical search for the agent eventually unearthed the source—flying foxes, or fruit bats of the Pteropus genus.

Shortly after Hendra virus was identified, farmers began noticing a high incidence of fetal abnormalities and other reproductive disorders within two swine herds in New South Wales,
Australia. Diligent attention to virology yielded a novel virus from the pigs, and this virus was named Menangle. Workers associated with the pigs also came down with a flu-like illness and proved seropositive to the Menangle virus. The origin of this virus might have gone totally undetected had it not been for a camp of flying foxes next to the swine farms. Serosampling of this bat population revealed that they, too, were seropositive to the newly described virus, implicating them as the source of the emerging disease.

As scientists looked more closely at the sources of the Hendra and Menangle viruses and at people who may have been exposed to pteropid bats, the investigators learned that some humans engaged in bat rehabilitation had recently died from an unusual encephalitis. By examining archived specimens from bats, they detected another, albeit similar, virus in the brains of the flying foxes, that they named lyssavirus.

Thus, the Australians in a few years experienced three emergent zoonotic viruses, none of which had been described before—a remarkable and frightening occurrence. But this Australian bat trick was pale in comparison to what had been described before—vCJD among humans. Although hy-
disease (vCJD) cases soon termed variant Creutzfeldt-Jakob disease (vCJD)—that likely resulted when BSE transferred to humans. Thus, from an emerging disease of animals, we reap an emerging zoonotic disease. The Escher diagram with its intricate interconnectedness between human and animal figures resurfaces. To date, U.K. public health experts have documented more than 130 cases of vCJD, with most confined to Great Britain where many cases of BSE also occurred. However, BSE spread insidiously throughout Europe and also has been diagnosed in Asia. Moreover, vCJD among humans is arising in other countries. What will be the forthcoming configuration of the epidemic curve—a small blip or a hyperbolic disaster?

Other Emerging Diseases Involve Foodborne Pathogens

Several emergent foodborne diseases affecting humans originated in animals. Although hygiene has made quantum leaps since Virchow was working to decrease Trichinella in pork products, foodborne diseases in humans remain a major issue. Campylobacteriosis and salmonellosis primarily from poultry products, Escherichia coli O157:H7 from hamburger and other foods, and Listeria monocytogenes from meat and dairy products continue to prompt public health concerns. Campylobacter causes disease in about 2 million people per year in the United States, with Salmonella sickening another 1.3 million.

E. coli O157:H7 and L. monocytogenes cause more severe illnesses. Virchow never would have imagined how E. coli from the intestinal tract of one cow could contaminate tons of hamburger or how Listeria-contaminated deli meats from one packing plant could be disseminated to dozens of states. The scale of food production may increase efficiency and lower costs, but it also can lead to considerable public health problems.

Technological advances, undertaken in the name of improving agricultural production, can have untoward public health consequences. Bovine spongiform encephalopathy (BSE) took the regulatory world by surprise when it appeared in British cattle in the mid-1980s and was found to be spreading through contaminated feed. Public health experts came to recognize that recycling bovine proteins as feed to cattle gave rise to this outbreak. Such recycling has much to commend it in terms of improving food production efficiencies. Unfortunately, technological advances can have unexpected results.

After BSE emerged among cattle, a U.K. committee identified a series of human neurologic cases—soon termed variant Creutzfeldt-Jakob disease (vCJD)—that likely resulted when BSE transferred to humans. Thus, from an emerging disease of animals, we reap an emerging zoonotic disease. The Escher diagram with its intricate interconnectedness between human and animal figures resurfaces. To date, U.K. public health experts have documented more than 130 cases of vCJD, with most confined to Great Britain where many cases of BSE also occurred. However, BSE spread insidiously throughout Europe and also has been diagnosed in Asia. Moreover, vCJD among humans is arising in other countries. What will be the forthcoming configuration of the epidemic curve—a small blip or a hyperbolic disaster?
Companion Animals Another Source of Zoonoses

But it is not just global trade, habitat destruction, and food-processing changes that are responsible for the emergence of zoonotic diseases. Companion animals also sometimes serve as fertile hosts for agents that move into people to cause disease. Keeping companion animals has become extremely popular in the developed world. In the United States, for instance, more than 50% of households keep either a dog or a cat, a demographic phenomenon that Virchow would find surprising. In addition, keeping exotic pets is another well-established, but less-widely disseminated practice, with 2.5% of households harboring a pet ferret, rodent, rabbit, or reptile.

Various human health risks are associated with keeping pets—ringworm, scabies, salmonellosis, and visceral larval migrans are among the well-recognized syndromes. In recent years, other serious zoonoses attributable to companion animals have emerged.

People who are bitten or scratched by a cat can develop a syndrome known as “cat scratch disease.” Painstaking bacteriologic work led researchers to identify the etiologic agent, *Bartonella henselae*. Probably spread among cats by fleas, this microorganism causes a lengthy subclinical bacteremia in cats. But when it infects humans, it leads to a prolonged malaise, often accompanied by cervical lymphadenopathy. Disease is far more severe in immunocompromised individuals.

*Capnocytophaga canimorsus* is a fastidious organism, causing no visible disease in its canine host. However, when it gains entrance into humans through a bite or even simply when an animal licks an open sore, *C. canimorsus* can cause septicemia, leading to disseminated intravascular coagulation and peripheral gangrene. The mortality rate is quite high, again, particularly among the immunocompromised.

*Echinococcus multilocularis* is an intestinal cestode naturally found in Arctic carnivores, and now also in many dogs that overlap the range of these wild carnivores. The intermediate form grows as an oncosphere within parenchymatous organs of small rodents that ingest cestode eggs in the environment. When Arctic carnivores or domestic dogs eat these small rodents, the cycle is completed. Unfortunately, humans may also act as hosts for this intermediate form, which grows in multiple cystic spaces, predominantly in the liver.

That form of growth is termed malignant and, indeed, often by the time the disease is diagnosed, much of the liver has been consumed by the parasite. However, Virchow long ago elucidated the infectious nature of these “alveolar hydatid cysts,” which had previously been described as neoplastic. The prevalence of alveolar hydatid disease among humans continues to increase, making it a significant public health issue in many areas. Much of this increase is due to humans moving into more northerly climes with their domestic dogs, and also to translocations of Arctic carnivores to restock depleted southern preserves.

Bubonic plague, a disease thought by many to be relegated to history books, in fact is still in its third global pandemic and is well established in the western United States. For Americans, the greatest risk of plague comes from companion animals. As people with their rodent-seeking pets move into areas of endemic sylvatic disease, the risk of developing this disease increases because their pets may carry the disease or transport *Yersinia pestis*-carrying fleas. During the past 30 years, there have been 300 U.S. cases of *Y. pestis* infection in cats and many cases in humans as a result of contact with infected cats.

Can Zoonotic Outbreaks Be Forecast?

As the human population continues to expand and hop from continent to continent, as we mix various species together for trade, personal satisfaction, or technological advances, what does the future hold? Is there a microbiologic crystal ball to predict the next major zoonotic disease?

Sarah Cleaveland of the Centre for Tropical Veterinary Medicine at the University of Edinburgh in Scotland provides interesting insights into possibilities for the future. She carefully catalogued 1,415 known pathogens of humans, 616 known pathogens of domestic livestock, and 374 known pathogens of domestic carnivores. Of those pathogens of humans, 61.6% have a zoonotic origin. Of the 616 pathogens of domestic livestock, 77.3% are considered “multihost,” while 90% of the 374 pathogens of carnivores are considered multihost.

Thus, sharing microbes that have cross-infecting abilities seems the norm. Because the major-
ity of microbes can—and do—inflect multiple hosts, we will undoubtedly see new diseases emerge. Moreover, with so many pathogens in wildlife, we can expect additional pathogens from that quarter eventually infecting domestic species and humans.

As we continue to intermingle various animal species, new diseases will surely arise. Advanced nucleic acid technologies may make it possible to identify organisms that resist cultivation and to learn more about pathogens in animals about which we know little or nothing. David Relman of Stanford University, Stanford, Calif., and his collaborators, using sequence-based methods to identify bacteria, estimate that we can cultivate only about 0.4% of the bacteria in the natural world.

In particular, Relman’s work on the ecology of the human subgingival crevice highlights its exceptionally high degree of bacterial diversity. In fact, most DNA sequences for microbial species from this niche do not match any known bacterial sequences in accessible databases. If this is the case for microbes within the human oral cavity, a host species microbiologic niche that has been intensively studied, what will be the case for, say, the gastrointestinal system of the domestic cat, or iguana, or hedgehog? And, how many of those microorganisms might find the human body a hospitable environment in which to replicate and cause disease?

In today’s world, animals and people are connected and interconnected. These connections are fluid, with lines constantly moving and shifting, as global trade, habitat change, and a myriad of lifestyle issues surface and evolve. As we further industrialize our agribusiness enterprises, undertake ecotourism to view endangered species, import billions of tons of foodstuffs from around the world, move llamas into the Rocky Mountains, and sell prairie dogs in pet stores (a practice that public health officials recently sought to halt), one conclusion remains certain. Additional zoonotic diseases will emerge.

In fact, the interface between animal and human health is becoming blurred to a point of indistinction. We face a huge challenge in being prepared to recognize and respond to each new emerging zoonotic disease. Virchow’s initial call to consider one medicine is more relevant than ever. Only with a strong interdisciplinary understanding of diseases and microbial ecology can we hope to be prepared.

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