Pioneer Science and the Great Plagues

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Published by Purdue University Press

Cheville, Norman F.
Purdue University Press, 2021.
Project MUSE. muse.jhu.edu/book/84018.

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replaced by Dr. Harley Moon, who removed the head of the NADC Brucellosis Research Group and replaced him with me. The mandate was to achieve the leadership, management, and research plans required for development of a killed Brucella vaccine against brucellosis in cattle. The first meeting with the NCA was brutal. A member from Texas publicly noted the research failures and demanded progress, saying, “You guys in Iowa are sitting on your ass doing nothing.” The cattlemen were insisting that a killed vaccine be produced. To be fair, there had been no progress.

Testifying at a U.S. House Agricultural Committee special meeting, an agricultural research scientist explained that a killed vaccine would not work; the congressmen were promised that a new live vaccine could be produced in five years using a mutant strain that lacked the lipopolysaccharide component that reacted in the field test. Bacterial candidates for use as a vaccine were screened: Were they safe? Did they persist for long enough to produce immunity? Did they cause human infection? Experimental designs for a progressive system of testing of candidate strains revealed a superior candidate: RB51, a natural mutant discovered by Gerhard Schurig, a scientist at Virginia Tech University. In tests to determine immunogenicity and protection, RB51 was clearly effective. The contract for production was written for the Colorado Serum Company in 1995, meeting the goal of five years as promised to the NCA.

34. OLD PLAGUES IN THE WILD: THE NATIONAL WILDLIFE CENTERS

Brucellosis in bison in Yellowstone National Park had smoldered for years—it was first reported by the Bureau of Animal Industry’s John Mohler in 1917. In the 1920s, forest ranger veterinarians began to vaccinate bison with live brucellosis strain 19 vaccine. Persistent objections from Indian tribes and recreational groups led to the abandonment of bison vaccination. Then the National Park Service’s postwar operational change to a natural environment policy—without human interference of any kind—increased brucellosis in Yellowstone bison. National Park Service officials never observed abortion in bison; despite a high number of bison with positive blood tests for brucellosis, they insisted that infected animals in the park did not abort. But they did. Brucellosis can only be maintained in wild elk and bison by abortion—the billions of bacteria on
infected placentas are licked by new hosts. Bison give birth unobserved at night and aborted fetuses are eaten by scavenging carnivores before morning.

The problem was that infected bison migrating outside the park to the north could infect cattle in the Paradise Valley of the Yellowstone River—keeping Montana ranchers in an expensive perpetual state of quarantine and mandatory vaccination, and the U.S. Department of Agriculture from declaring the nation’s cattle free of brucellosis. In the winter of 1996–1997, Yellowstone herds had more than thirty-four hundred bison; 30 to 40 percent of them reacted positively in laboratory tests for brucellosis. Only 1 to 2 percent of the large elk population in the park had positive tests. Harsh weather that winter forced record numbers to starve and others to leave the park in search of forage. National attention focused on management strategies—including shooting bison—used to prevent spread of the disease from bison to cattle that grazed on lands adjacent to the park.

In 1997, Secretary of the Interior Bruce Babbitt asked the National Academy of Sciences to undertake a six-month study of brucellosis in the Greater Yellowstone Area—the GYA—to look at the issues, including the extent of
bison infection and potential for a vaccine program and the transmission of *Brucella abortus* among cattle, bison, elk, and other wildlife. The official position of the National Park Service was that brucellosis did not cause infected bison to abort their fetus—a troubling stance. The study began as “Brucellosis in the Greater Yellowstone Area.” To expedite matters, the National Academy of Sciences used a new paradigm. Instead of a committee of experts, it used a new approach: there would be only two experts who would interview all parties involved. The coauthors were to be a veterinary scientist (me) and mammalian ecologist, Dale McCullough, a professor of wildlife biology in the Department of Environmental Science at the University of California, Berkeley."

The plan was to have informational meetings for input of concerned citizens in each of the states in the GYA—Wyoming, Montana, and Idaho. Controversial from the start, there were several major power bases attempting to influence the direction of the study. The two major players were the National Park Service and the U.S. Department of Agriculture, but there were powerful groups on the periphery: state Departments of Agriculture and Departments of Wildlife Conservation from states surrounding the park. There was strong support from ranchers, state livestock organizations, and the State Veterinarian’s Offices from Wyoming, Montana, and Idaho. There were equally strong rejections by Indian tribes, recreationalists, and elk hunters.

The study held informational meetings in Bozeman, Montana, Jackson, Wyoming, and Idaho Falls, Idaho. The first of these was on the campus of Montana State University. Security was tight, and the campus police had a presence in the auditorium. One in the audience had thrown bison feces on the Montana governor the previous week, but nothing was tossed and the meetings went well. What we found was that brucellosis was infecting GYA bison and that the possibility of transmission to cattle was high. Elk were another matter. Although brucellosis is not readily transmitted in nature because pregnant elk sequester during birthing, Wyoming has state-sponsored feed grounds where elk congregate in winter and give birth in high population densities, making them a serious threat for promoting infection. The study received good reviews. Over the next two decades elk became the major source of brucellosis in the GYA, requiring yet a third study by the National Academy of Sciences.

**Rabies persists in nature** with a unique strategy. How rabies virus survives and propagates in wild animals was reported in 1969 by scientists Frederick Murphy and Richard Diercks at the Communicable Disease Center
in Atlanta. They discovered that in foxes, bats, and other biting animals, rabies virus replicates to large amounts in two sites: the salivary glands and the brain. Brain infection induces a change in the normal fearful or avoidance attitude of the host to one of aggressive behavior in which, in carnivores at least, the host will attack and bite potential hosts. In the salivary glands, large amounts of rabies virus are produced—new viruses budding from the glandular cells into the lumen of salivary ductules are released into the saliva, which during an attack by a rabid animal maintains rabies virus in nature.

Rabies vaccination programs in dogs were begun during the 1940s and 1950s and effectively controlled, and even eliminated, the circulation of canine rabies in North America. But that did not solve the problem. Rabies was being maintained in nature by wildlife. As the incidence in humans and domestic animals declined, the danger of wildlife remained. Since 1990, 24 of 26 human cases of rabies have been associated with rabies virus variants maintained by bats; only 2 of these cases involved a report of a definite history of an animal bite; for the rest, the likely route of infection was transmission by bite during contact with a bat that was ignored, unnoticed, or forgotten. The incidence of rabies in wild mammals in 1996, as determined by cross-sectional analysis of passive surveillance taken from data of state and territorial public health departments, showed that of 4,454 cases of animal rabies, 91 percent involved wildlife species. During 2017, 24,458 bats were tested; 5.9 percent were confirmed as positive for rabies. Those numbers, although fluctuating according to rabies virus variants, are close to the same data from today.

Mixing rabies vaccine in small packets of food disguised as bait and delivered in the wilderness by airplane has proven effective. In Switzerland, use of baited oral vaccine for two decades resulted in a rabies-free status in 1998; the same procedure was successfully used in France into 2000. In Canada, a program started in 1985 led to substantial decreases of reported cases of rabies in fox populations. In the U.S., sixteen states, most along the Appalachian Mountain chain from Alabama and Georgia to Maine, have used oral rabies vaccines for raccoons.

Reemergence of a canine rabies variant virus in South Texas during the later 1970s led to the use of oral vaccines along the Rio Grande River, a program that reduced the spread of rabies in coyotes and gray foxes, and from them into dogs. Use of a recombinant vaccine, vaccinia virus bearing a rabies glycoprotein—targeting raccoons and gray foxes as well as coyotes in Texas—has shown
promise. In Texas, state regulations that prohibited translocation of wild species for hunting helped to reduce accidental spread to unaffected areas.

**Fowl Plague, a European Disease** of poultry that was new to the U.S., broke out at a live poultry market in New York City in 1924. Rapidly developing signs of respiratory difficulty and pneumonia were brief and lethal; a massive number of birds died within hours after being infected. The source of the virus was traced to vials of fowl plague virus that had been imported in 1923 by a laboratory scientist working on unidentified filterable viruses. The disease was eliminated by the removal of sick birds and quarantine but had rapidly spread—in most cases by contaminated railcars—to New Jersey, Connecticut, and Pennsylvania. By April 1925, fowl plague had spread to the Midwest—to Indiana, Michigan, West Virginia, Missouri, and the Chicago suburbs. The fowl plague virus had come from Europe, and there were outbreaks there again in the 1950s. The mystery of fowl plague virus was solved when in 1955 virologist Werner Shäfer in Germany reported it to be a type A influenza virus.

In the twentieth century there were four pandemics of human influenza, each identified by the letters H and N, used by scientists to identify the variance of two proteins; the symbols are for viral surface proteins that are important for the virus to infect respiratory tract cells—H for hemagglutinin, used for attachment to host cells, and N for neuraminidase, to support release of progeny virus. The influenza virus causing the pandemic of 1918 was H1N1; in the pandemic of 1957 it was H2N2, and in 1968, H3N2—both less dangerous than the 1918 virus. Then, in 1977, a reappearance of the H1N1 flu virus brought near panic to public health officials—unjustified, as it turned out—who feared the return of the massive human deaths of 1918.

The real significance of all this came in the 1970s when Robert Gordon Webster, New Zealander farm boy turned virologist at St. Jude’s Children’s Hospital in Tennessee, proposed that influenza virus genes were being recombined—a process called genetic recombination—to increase virulence, and in the process, endowing the new virus strain to move into new animal species. Input into the story had come from Hélio Pereira, Webster’s mentor at the National Institute for Medical Research in London, and from veterinarian Bernard Easterday at the University of Wisconsin—who demonstrated the natural transmission of swine influenza from pigs to humans. In the end, migratory aquatic wildfowl were discovered to have globally spread the fowl plague
The ability of influenza viruses to rapidly mutate according to the needs of their avian or mammalian hosts was an astonishing revelation. The impact of wildlife on human influenza started with the Asian flu outbreak in humans during 1957–1958. It had been caused by a new strain H2N2 that contained genes from avian influenza. A decade later, the flu pandemic of 1968–1969 in which one million people died was caused by an influenza virus with yet another mutation in its neuraminidase, H3N2, and appeared to have arisen from an antigenic shift from the avian genes of the 1957 virus. The outbreak was first reported in Hong Kong on July 13, 1968, and by September had spread into Vietnam, Singapore, India, and the Philippines. Soldiers returning from Vietnam brought the virus to California, and by December of 1968 it had become widespread throughout the U.S. In the next year, thirty-eight thousand Americans died of influenza. It was clear that the story of influenza in humans began in the Orient and involved intercontinental migratory pathways of birds. Wild aquatic birds infected with viruses that carried the full variety of influenza A virus genes were the natural reservoir—new influenza strains were arising from the genetic recombination of viral genes in a partially immune host with a mixed infection of two different influenza viruses.

Plague is the rat flea–transmitted bacterial disease that caused the massive death loss in Europe in the 1300s; bubonic plague, aka black death, appeared as skin blotches from internal bleeding and lymph node swellings the size of eggs in the groin and armpits that oozed pus and ulcerated to produce boils. Plague persists in wildlife in North America in reservoirs of rodents. Existing largely in prairie dogs, chipmunks, and ground squirrels, sylvatic plague can spread to less susceptible species such as dogs, coyotes, and other Canidae that, although relatively resistant, have a close relationship to wild rodents. In contrast, cats, bobcats, mountain lions, and other Felidae are especially susceptible and will develop pneumonic plague, the pattern of disease in black death. The bacterium that causes plague, *Yersinia pestis*, is scary in the U.S., partly because of its designation as a Class A bioterror agent by the Department of Homeland Security.

Plague has been monitored by a unique laboratory for the study of wildlife health, the Smithsonian Conservation Biology Institute (SCBI), which was established in 1974 as a unit of the National Zoo to be used for zoological research.
and studies on captive reproductive physiology. One component, the Global Health Program, is run by veterinary scientists who monitor and investigate infectious diseases in wildlife. Their interest is anthrax, a serious problem in Kenya, and their research is centered on Gray’s zebras and how vultures, with their astonishing tolerance of animal pathogens, might spread the disease. SCBI’s location, the site of the Front Royal Remount Station constructed when Congress purchased forty-two farms in the area for a Quartermaster Corps Remount Station in 1909, is a unique heritage for its veterinarians.  

Endangered species and problems with their reintroduction into the wild is a major issue with the SCBI, particularly in the return of the black-footed ferret, which faced extinction from a combination of canine distemper and loss of food and habitat. Canine distemper has been associated with mass mortalities in red pandas, palm civets, raccoons, African wild dogs, Island foxes (in California), Amur tigers, and African lions in the Serengeti. A big problem is that the protection of one species often leads to the destruction of another.

Black-footed ferrets depend on prairie dogs for their diet and disappear when their food source is destroyed. The black-tailed prairie dogs—herbivorous rodents in western grasslands—experience short epizootics of plague that result in widespread die-offs interspersed with periods of plague inactivity. Plague is carried by fleas and their astonishingly rapid multiplication cycles. To save the ferrets, fleas were killed by spraying potent insecticides into prairie dog burrows; fleas were killed but so were all other insects. Prairie dog burrows are a food source for a suite of bird species; when their insect food supply was destroyed, the mountain plover disappeared.

Duck plague, a herpesvirus disease new to the U.S., killed forty thousand waterfowl in the fall and winter of 1972–1973; by January, 40 percent of the one hundred thousand mallards had died while overwintering at the Lake Andes National Wildlife Refuge in South Dakota. Adding to the problem was that survivors became carriers of the disease, spreading duck plague along the flight paths. Throughout the region, state fish and game facilities could not deal with a problem of this magnitude, and the National Wildlife Health Center was opened in 1975 in Madison, Wisconsin—a state with a strong history of wildlife disease research—with the mandate to prevent, control, and investigate wildlife diseases. Today, the NWHC is involved in many serious environmental
problems, including lead shot poisoning, plague, botulism, chronic wasting disease in deer, and oil spill toxicity in eagles, seabirds, and harbor seals. Inexplicably, the new NWHC was placed within the U.S. Geological Survey in the Department of Interior—a political move that separated it from the scientific veterinary expertise in the Agricultural Research Service.

Few academic institutions investigated wildlife disease in the 1960s. Colorado State University maintained an active wildlife group that led research on chronic wasting disease. At the Ontario Veterinary College, an impressive wildlife disease unit was active with Lars Karstad, who reported a new disease of deer, epizootic hemorrhagic disease; Karstad’s career included African wildlife as well as diseases of marine animals. The Department of Veterinary Science at the University of Wisconsin, as in several other states with ample wildlife habitats or inland waterways, began to be active in infectious diseases of mammals and fish. Washington State University developed an active program on the diseases of fur-bearing animals in cooperation with the federal government. Two of their scientists—John Gorham and Donald Cordy—discovered the rickettsial cause of salmon poisoning in dogs and foxes.

Chronic wasting disease remains a serious threat to both wild and domestic elk and deer in North America. Insidious, with very long incubation periods, the uniformly fatal neurologic disease has overtones of paralytic disease for other species. The National Wildlife Research Center, a component of the USDA’s Animal and Plant Health Inspection Service, is a modern research laboratory in the foothills campus of Colorado State University that can track chronic wasting disease. Its program surveys and undertakes field investigations on rabies, influenza, tuberculosis, plague, and tularemia in wild birds and mammals.

Many infectious diseases are maintained in nature by arthropod vectors—mosquitoes, flies, and ticks—which are monitored by federal and state laboratories, including the Centers for Disease Control and Prevention, the Center for Vector-Borne Disease at the University of Rhode Island, and the National Center for Veterinary Parasitology at Oklahoma State University. In North America, the blacklegged or deer tick, *Ixodes scalpularis*, is a vector for many of the most serious tick-borne diseases, including anaplasmosis, ehrlichiosis, and Powassan virus disease. It is the primary carrier of the bacterium *Borrelia burgdorferi*—the cause of Lyme disease in dogs, horses, and humans—and is one of the fastest growing infectious diseases diagnosed in the U.S.
The number of canine Lyme disease cases recorded increased from 250,000 in 1915 to nearly 350,000 in 2019—paralleling similar increases in canine anaplasmosis and ehrlichiosis. Lyme disease is notoriously difficult to diagnosis in dogs, and the actual infections may be ten times that number. Most dogs exposed to *B. burgdorferi* develop only subclinical infection, and those that become sick show vague clinical signs of anorexia, lethargy, and depression. Appearing in the veterinary clinic with fever, swollen joints, and enlarged lymph nodes, Lyme disease in dogs is difficult to assess.

Prior to 1970, the blacklegged tick was not viewed as an important vector of disease. Agricultural deforestation, as well as hunting and habitat loss of white-tailed deer, the primary host, restricted the tick to the Northeast and Upper Midwest. After World War II, the increasing creep of suburbia into the forested Northeast with the reforestation of farmland led to recovered deer populations; this, in concert with climate change—milder winters, earlier springs, and warmer summers—promoted the blacklegged tick.

**BATS ARE BIOLOGICAL SUPERVILLAINS.** A diverse group—over twelve hundred species, second only to rodents among mammals—they harbor more dangerous viruses for animals and humans than any other. Bats are natural reservoirs for rabies, Ebola and Marburg viruses, the paramyxoviruses Hendra and Nipah, and the coronaviruses SARS, MERS and, in 2019, the SARS-2 (that causes the disease COVID-19 that occurs in humans and mink). Evidence is emerging that the destructive nature of SARS-2 is tied to its sneaky use of the body’s normal receptor molecules for angiotensin-converting enzyme—a messenger molecule present on blood vessel surfaces in lungs, kidneys, and heart used to control blood pressure.

Most coronaviruses are passed through an intermediate host to infect humans: severe acute respiratory syndrome (SARS) appeared in 2003 when horseshoe bats infected Himalayan civets and raccoon dogs sold for meat in Wuhan, China; Middle East respiratory syndrome (MERS) arose in Saudi Arabia in 2012 when the host was the dromedary camel. Just as the bird-pig-human progression leads to human influenza, the bat-camel-human progression (with its 35 percent fatality rate) led to MERS.

Animal coronaviruses rarely need an intermediate host: infectious bronchitis in chickens, porcine epidemic diarrhea virus (PEDV), and swine acute diarrhea syndrome (SADS) coronaviruses do not require other species for transmission.
In cats, the coronavirus that caused mild feline infectious enteritis changed through genetic recombination to the lethal coronavirus of feline infectious peritonitis. They are scary viruses; the genetic codes of coronaviruses have high rates of mutation and genetic recombination.

Ecological surveillance reveals that intraspecies coronavirus transmission occurs when pulses of high levels of virus occur in bat populations and a “spill-over phenomenon” occurs that infects other species. Seasonal epidemic cycles can be brought on by stress from nutritional deficits, reproductive adversity, and intercurrent disease. The omnipresence of bats—they are 20 percent of all mammals—coupled with our ignorance of how their immune systems work, makes them a high risk for pandemic emergence of host-adapting coronaviruses.

35. NEW PLAGUES: SCRAPIE, MAD COW DISEASE, AND THE PRION

For two centuries, farmers in Scotland had lost sheep with a progressive brain disease they called scrapie—so named because in the first stages of disease affected sheep would scrape their skin raw against trees and fences. Soon the scraping sheep would walk with a bunny-hop gait, their hind limbs uncoordinated with the front—a high-stepping gait like a donkey trot, unable to extend the hind fetlocks. Then there were tremors of the head, grinding of teeth, and finally an inability to stand, paralysis, and a prolonged death.

Scrapie was endemic in black-faced British breeds of sheep and was being diagnosed in Iceland, France, and Germany in sheep imported from Britain. After World War II, scrapie appeared throughout the world’s sheep-raising areas: Canada in 1946, then Australia and New Zealand and the U.S. in 1947—by October, scrapie was diagnosed in seventy flocks in nineteen states. The disease occurred only in sheep over eighteen months old. Although at first glance it seemed to be inherited, it did not follow a pattern of Mendelian inheritance. Despite multiple attempts, no virus, bacterium, or any other infectious agent could be identified as causal, yet scrapie appeared to be passed to flock mates and newborn lambs. Proving what field veterinarians already suspected, Scot scientists at the Moredun Institute near Edinburgh transmitted scrapie from sick to normal sheep.