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.
Scottish and Icelandic veterinary pathologists, examining brains from affected sheep, documented what was going on. Neurons, the body-controlling cells in the brain, were dead. Dying neurons formed large vacuoles, making the brain tissue look like a sponge. The scientific term they applied to this spongy brain affliction was transmissible spongiform encephalopathy—TSE for short. Still disconcerting was that no evidence of a virus was found. But then, scrapie was not associated with human disease. Scots had been eating mutton, cooked and rare, muscle and brain, for over a hundred years and there had been no evidence for a scrapie disease in humans. Scrapie was an outlier. There was nothing else quite like it.

In the 1950s, veterinarian Dieter Burger, working toward his PhD at the University of Wisconsin, drove north to visit a mink farmer in Barron, Wisconsin, whose mink were dying from a progressive neurologic disease. The mink had developed abnormal behavior that began with disorientation and stumbling and ended in paralysis and death. Examining the brains of dead mink, Burger found spongy, vacuolated changes, noting that they were similar to scrapie in sheep; he called the disease mink encephalopathy. It was the second description of what was soon to become a really scary group of diseases.

Then came news of a degenerative neurologic disease of the cannibalistic Fore people in New Guinea that began with trembling, slurred speech, and unsteady gait. Victims wasted away, finally dying after paralysis and coma. Uniformly progressive and fatal, it was thought by the tribe to be due to sorcery from ancestral ghosts. By the 1950s it was killing about two hundred members each year, mostly women and children. Tribesmen called the affliction cassowary disease, confusing the wasting aspects of the disease with tuberculosis. Cassowaries are large ratites, flightless birds that lack a keel bone. They are aggressive and dangerous because of their razor-sharp claws and have been known to kill humans; and cassowaries have a high incidence of tuberculosis.

Australian patrol officers in the area reported the disease to Canberra, calling it kuru, the Fore word for shivering, and noted that it might be a hereditary mental condition. Kuru was found only in the Fore tribe, whose ritualistic funerary cannibalism involved relatives preparing and eating tissues of deceased family members. Men ate the muscles and liver while consumption of the brain was relegated to women and children.

In the 1950s the American medical scientist Daniel Carleton Gajdusek, in Papua New Guinea to observe kuru, began looking for plant toxins as plausible
causes. The significant lead in Gajdusek’s study of kuru was pointed out by the veterinary pathologist William Hadlow: “On the similarities of two progressive degenerative disorders of the central nervous system — namely scrapie affecting sheep, and Kuru affecting the Fore natives in the Eastern Highlands of New Guinea . . . their overall resemblance is too impressive to be ignored.”

Following Hadlow’s clue, investigators began to use sheep scrapie as a model for kuru, and both would become models for the rapidly expanding species range of the TSEs. Soon added to the TSE list were Creutzfeld-Jakob disease in humans, chronic wasting disease in deer and elk, and a new and terrible disease in Britain, mad cow disease.

CJD, shorthand for Creutzfeldt-Jakob disease, was a very rare, spontaneously occurring human fatal neurodegenerative disease which, like scrapie, had no causal agent and fit no pattern of genetic inheritance. But by the mid-1950s, it was clear that CJD, although arising spontaneously, could be passed from patient to patient when inadvertently introduced into the brain or eye by contaminated medical instruments. It was resistant to disinfectants. Clusters of human CJD appeared years after patients had corneal transplants, implantation of brain electrodes, or other probes that had been used on a previous patient with CJD. Whatever was causing CJD was not destroyed by common hospital sterilization procedures and was being transmitted from one patient to another.

In the mid-1960s, Colorado research scientists began seeing a strange neurologic disease — they were calling it chronic wasting disease. Affected deer appeared to be starving and stumbling with an abnormal gait. Unable to swallow, they inhaled their feed, and many were dying of aspiration pneumonia. The disease had appeared in a closed herd of captive mule deer in the Denver Zoo and in deer penned in research facilities in Fort Collins — deer that had been captured on the western mountain slopes.

The Denver Zoo had sold deer to the Toronto Zoo, where in 1978 veterinary wildlife pathologist Ian Barker at Ontario Veterinary College saw microscopic lesions in the brain of dying deer that he noted were similar to those of scrapie in sheep. Beth Williams — who had graduated DVM from Colorado State and had taken a residence in zoo medicine in Toronto — examined Barker’s histologic slides. Returning to Colorado State to begin a graduate program in veterinary pathology, she began her studies in chronic wasting disease. It was the beginning of a distinguished career; in 1980 Williams reported chronic
wasting disease as one of the TSEs. The next year, Terry Spraker at the Colorado State Veterinary Diagnostic Laboratory found elk with chronic wasting disease in Rocky Mountain National Park. No one was paying much attention—not even deer hunters.

Then, the real horror stories began. With some press drama, mad cow disease was reported in England. Veterinarians were calling it bovine spongiform encephalopathy. First appearing in British cattle in the 1980s, it was believed to have started when cattle were fed meat and bonemeal containing abattoir brain tissue from sheep with scrapie. Affected cows were first noticed to have an abnormal gait, tremors, hyper-responses to stimuli, and other behavioral changes. Progressing to paralysis and death, thousands of cattle were afflicted and died in Britain and then in France. The official eradication that ensued, which required the killing of thousands of cattle and the burning of carcasses, led to public fear, export bans, and worldwide adverse publicity.

The scariest disease of all—for people at any rate—was the discovery that an unusually large increase of neurologic deaths in Britain of rapidly progressive CJD was related to eating brain tissue from cows with mad cow disease. The new human disease, called variant Creutzfeldt-Jakob disease, had been first noted in Britain in 1987 and shown to be acquired from eating sausages that had been processed to include the brains and spinal cords of cattle that had bovine spongiform encephalopathy. The troublesome thing was that the numbers of patients were rising rapidly; more than 175 people would be dead by the end of the decade before the disease had been stopped. There was some controversy about how the disease had begun—in 2005 Alan Colchester, a neurologist at the University of Kent, suggested that the source of bovine spongiform encephalopathy in cattle was not scrapie from sheep but the CJD prion that had been imported in bonemeal from India that contained human tissues of Indian patients with CJD.

The breakthrough to understanding the TSEs came in 1982, when Stanley Prusiner at the University of California San Francisco presented evidence that the infectious agent of scrapie was not a virus that contained instructional genes—the agent had no genetic templates of DNA or RNA. Turns out, it was a misfolded protein Prusiner called a prion (he designated the prion protein in scrapie PrP\textsuperscript{Sc}). PrP\textsuperscript{Sc} had originated from a corresponding normal body protein, PrP\textsuperscript{c} (“c” for cell), that had become improperly folded. Prusiner did not know the normal function of PrP\textsuperscript{c}, and although scientists discovered it to be a protein
that is inserted in the brain’s neuron surface membrane, its activity still remains mysterious.

The prion was an astonishing concept. Prions lacked genes, components assumed necessary for an infectious agent to replicate—there was no DNA or RNA, the nucleic acids required for transmission of genetic information. Prions “infect” a new host and cause disease by blocking a normal protein; inserting themselves, they act as surreptitious templates to cause a normal protein to be folded improperly into a misfolded version that does not function, cannot be degraded for removal, and accumulates inside the brain cells to cause mischief.

The normal PrPc molecule was found to be relatively unstable—an alpha helix—and the greater stability of the misfolded version, PrPSc, allows it to become the dominant template and take over the protein synthesis pathway for PrPc. Progressive accumulation of the PrPSc causes it to aggregate inside the cell and to polymerize outside the cell into PrPSc amyloid, tightly packed beta sheets that assemble into amyloid fibrils that can be seen with the electron microscope. Damage results when the abnormal protein accumulates and kills neurons and polymerizes outside the cell as amyloid fibrils around tiny blood vessels.

It was clear that scrapie prions were dangerous misfolded proteins that could arise by spontaneous mutations, and once formed could be passed to other animals in contaminated needles and instruments. It was also discovered that when first transmitted, the prion protein replicated in the lymphoid tissues of the intestine and then spread to the brain—a discovery that made possible a diagnosis of TSE by biopsy of the rectal lining cells to detect PrPSc. At Iowa State University, Heather West Greenlee, doing research on the eye, discovered that these misfolded proteins affected retinal cells and that ophthalmic examination could be used as a diagnostic tool before the nervous signs of disease appeared. How prions kill neurons is a hot topic in neuroscience research—much of it applicable to human diseases like Parkinson’s and Alzheimer’s.