Pioneer Science and the Great Plagues

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Published by Purdue University Press

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Purdue University Press, 2021.
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Veterinary scientists hired by leading cancer centers made major contributions to feline leukemia. William David Hardy Jr., working in the Laboratory of Veterinary Oncology at Memorial Sloan Kettering Cancer Center in New York City, developed diagnostic tests for FeLV as well as other small animal diseases. Hardy’s work began with investigations on the transmission of FeLV in randomly selected outbred populations of cats.\textsuperscript{11}

Veterinarian Myron Elmer “Max” Essex in the School of Public Health at Harvard University was beginning his research that linked immunosuppression to retroviral infections in animals and humans.\textsuperscript{12} Essex received the Lasker Award jointly with the discoverers of human immunosuppressive virus (HIV). AIDS, short for acquired immunodeficiency disease syndrome, had been first reported clinically in June 1981 in five drug-using male homosexuals with rare pneumocystis pneumonia; two years later, the American Robert Gallo and French Luc Montagnier had independently reported in the same issue of \textit{Science} the discovery of a retrovirus they believed to cause AIDS. For the next decade, veterinarian Essex, working at Harvard and in Africa, made an astounding spectrum of discoveries that included simian T cell leukemia virus (STLV) and simian immunosuppressive virus (SIV), as well as the human immunosuppressive virus-2 (HIV-2) and the surface protein gp120 that is used in blood screening for HIV infection. Human HIV appears to have evolved in humans infected with the simian viruses in West Africa. Appointed chair of the Botswana-Harvard AIDS Institute Partnership, Max Essex is perhaps the most awarded veterinarian for scientific research for discoveries that linked leukemia and immunosuppression.

33. GRASSROOTS MANDATES: THE NATIONAL RESEARCH CENTERS FOR LIVESTOCK DISEASES

Fort Terry, an abandoned military base on a tiny island off the eastern tip of Long Island, eighty miles east of New York City, was deeded to the U.S. Department of Agriculture in the early 1950s. The USDA’s Agricultural Research Service built the new Plum Island Animal Disease Center, dedicated to protecting the livestock industry through research on foreign animal diseases—pestilences that would be disastrous if moved into North America. The major project was foot-and-mouth disease—dangerous because of its catastrophic
impact, extreme infectiousness, and highly variable genetic makeup—making vaccine production difficult and often ineffective. The unit would also investigate African swine fever and other dangerous foreign animal diseases and maintained a scientific staff at the ready for any global emergency. The new Plum Island facility had some drawbacks: the site required the USDA to operate a navy to move employees and animals into the site, and its limited mandate did not alleviate the overcrowded research buildings at the Beltsville labs outside an increasingly congested Washington, D.C.

To place research closer to the problems in the field, Congress provided funds in the 1960s for the Agricultural Research Service to establish laboratories in the Great Plains, Palouse, and Intermountain regions: the Veterinary Toxicology and Entomology Research Laboratory near Texas A&M University, the Animal Disease Research Unit at Washington State University in Pullman with John Gorham in charge, and the Poisonous Plant Research Laboratory near Utah State University in Logan. Some of these laboratories made striking discoveries. In Utah, pregnant sheep grazing *Veratrum californium* gave birth to lambs with cyclopia (a single median eye) when ingesting the plant only on a very precise date: the fourteenth day of gestation. To study respiratory disease in chickens, Funds for the South established the Southeast Poultry Research Laboratory in Athens, Georgia, in 1962; with the continuing importance of avian influenza, the lab developed diagnostic tests that became a critical link in protection of the poultry industry under the direction of veterinary virologist Charles Beard.

In 1956, a report titled *Veterinary Medical Science and Human Health* released by the subcommittee of the House Appropriations Committee chaired by Hubert Humphrey determined that approximately $65 million a year was being spent by the federal government on veterinary services and that new research facilities were needed. Veterinary facilities at the Beltsville Agricultural Research Center were badly out of date (and developers and other government agencies coveted the prime urban agricultural land at the site). The subcommittee approved a new animal disease laboratory at a cost of $20 million to be located near a school of veterinary medicine and authorized a ten-person committee to select a site.¹³

The final decision had been between Iowa State and Colorado State. The report of the Investigative Site Committee stated that its choice of the Iowa location was based on Iowa State—that it was “an outstanding scientific center and would provide opportunities for cooperation between the laboratory and
college.” The quality of the graduate college, its outstanding library, and Iowa State College laboratories in basic sciences of biology, chemistry, physics, nuclear research, mathematics, and statistics were all reasons for the selection of Iowa. Furthermore, the facts that Ames was “far removed from any critical industrial areas” and was a good community with “excellent public schools” were convincing to the committee. “One of the strongest things favoring Iowa State,” Wilbur Plager of the National Swine Growers told the Ames Tribune, “is that Iowa State unquestionably is closer to all types of livestock and poultry production than any other institution.”

Funds for construction of the laboratory were included in an appropriation bill signed by President Eisenhower on July 27, 1956, and four days later the USDA and Iowa State announced that the new “Federal Animal and Poultry Disease Laboratory” would be located on the 318-acre site two miles east of Ames. For the director of the new laboratory, William A. Hagan, an internationally recognized scientist and dean emeritus of Cornell University, was selected. Hagan had published widely in both medical and veterinary journals on infectious diseases of livestock, including tuberculosis. Even so, the new position would be a difficult one.

Named at the dedication ceremony in 1961 the National Animal Disease Laboratory (and renamed the National Animal Disease Center [NADC] in 1973), it was to house cooperating units of the USDA. It would be the major laboratory of the Agricultural Research Service but would also house the regulatory Animal and Plant Health Inspection Service’s Veterinary Services Laboratory, which would appoint an assistant director. Turns out that despite good intentions, there was as much competition as cooperation. Director Hagan did not last long in the position; he died on February 1, 1963, at thirty-thousand feet while en route to London from Chicago for a meeting in Geneva. The Agricultural Research Service appointed the assistant director, Chester Manthei, as the new director. To attract new graduates into science, young veterinarians were given time off to work toward their PhD degree in microbiology, pathology, or physiology at a university of their choice—it was a science-driven mini–GI Bill of enormous long-term impact, one that was killed as a measure of cost cutting in the 1980s.

The National Animal Disease Laboratory, like all units of the Agricultural Research Service, planned its research program through consensus of three forces: the scientists doing the work, the administrative National Program Staff housed in Washington, and national organizations of livestock producers,
which influenced congressional budget allocations. Once each year these three groups got together to strategize at the American Animal Health Association annual meeting. There, scientists presented their research data, producer groups prioritized their needs, and the regulatory agency responsible for field programs, the Animal and Plant Health Inspection Service (APHIS), adjusted their programs. When decisions were reached, administrators of the National Program Staff approved budgets for the research program for the coming year. It was a remarkable interaction that worked well, an unacclaimed jewel of the U.S. government. It was often confrontational but always effective. Each producer group held its own session, listened to research reports from scientists, and decided where its push for congressional money would be directed. In the 1960s, their needs were clear.

National Pork Producers: Eradicate hog cholera. The serum and virus vaccine of William Niles and Marion Dorset had eliminated hog cholera as a major threat, but vaccination was expensive. The threat of a disease breakout remained. After World War II, large swine confinement operations began to appear that were causing producers to promote an eradication program. In the 1950s, the USDA’s APHIS proposed that hog cholera be eradicated—Canada had eradicated hog cholera. Good idea, but there was a roadblock. The laboratory identification of hog cholera was expensive and time consuming—too slow and costly for a large-scale eradication program. Susceptible test pigs were given a suspect tissue suspension and observed for thirty days for signs of disease to confirm the diagnosis. The American Association of Veterinary Laboratory Diagnosticians had developed an elaborate systematic procedure as a guide to diagnosis—factors weighted according to their importance: herd history, clinical signs, lesions, and white blood counts; it was subjective and imprecise. After considerable lobbying by the producers, legislation was passed by Congress for a national hog cholera eradication program in September 1961.

At the National Animal Disease Laboratory, the problem was assigned to William Mengeling, who applied the new immunofluorescent antibody, or FA, test to detect hog cholera virus. In the microscopic FA test, specific hog cholera antibodies are tagged to fluorescein (which emits fluorescence when activated by ultraviolet light) and the labeled antibodies applied to a glass slide containing infected cell cultures or animal tissue. Attaching to the virus, the dye emits fluorescence that can be seen by the scientist. Fluids from blood or tissue specimens obtained from suspected hog cholera cases in the field were added and
allowed to grow to cell cultures; the positive FA procedure proved the presence of hog cholera virus. The test was adopted in state and federal laboratories and was the major factor in U.S. hog cholera eradication.16

*American Beef Association: Prevent* Escherichia coli *diarrhea.* Diarrheal disease was a major factor limiting red meat production in the 1970s; the bacterium *E. coli* was a major disease problem for calves and pigs throughout the world. It killed animals and was also a problem in food contamination, where it could kill humans. The NADC devoted one of its major units to *E. coli* research and hired veterinary pathologist Harley Moon to sort out this complex disease.17 Moon’s work defined how *E. coli* attached to intestinal epithelial cells in pigs, calves, and sheep and how it triggered cuplike indentations to facilitate bacterial attachment. His “attaching and effacing” entry mechanism was a new concept in enteric disease. Moon’s research would also lead to the use of vaccines based on fimbriae, the tiny surface hairs on bacterial surfaces. Fimbria-based vaccines proved highly successful in the protection of farm animals from *E. coli* disease.

Moon’s investigations found new strains of *E. coli* that produced an entero-toxin—a toxin that acted on the cells lining the intestine to block absorption and make them secrete excessive water into the gut to cause diarrhea. Loss of water and dehydration could kill the piglets. The relevance of enterotoxins came in 1993, when an outbreak of *E. coli* in humans arose from contaminated beef patties in seventy-three Jack in the Box fast-food restaurants in Washington, California, Nevada, and Idaho. Most victims were under ten years of age; four died of a new toxic hemolytic uremia syndrome, and many more were left with permanent kidney and brain damage. Health inspectors traced the contamination to the Monster Burger—billed as “so good it’s scary”—which had been cooked at a temperature too low for a time too short. The father of seventeen-month-old Riley Detweiler took up the cause, with constant press coverage, congressional hearings, and immediate action by the USDA, the National Cattlemen’s Beef Association, and the American Meat Institute, which transformed the national approach to meat safety.

*American Dairy Association: Control* mastitis and milk fever. Cows with milk fever go off feed, rapidly progress to tetany and collapse, and quickly develop changes in respiration that signal impending death. Drain of the mother’s calcium into her milk makes her own blood calcium drop to lethal levels. Milk fever appears at the onset of calving, when the cow is unable to mobilize enough
calcium to compensate for its loss at the beginning of lactation. It afflicted nearly 6 percent of dairy cattle in 1980 and cost the dairy industry a quarter of a billion dollars. The dairy industry made certain that the NADC was conducting prominent research in this area. Ron Horst and his colleagues discovered that milk fever was caused by an interplay of dietary calcium with potassium, sodium, and magnesium that disturbed the acid-base balance in blood, which in turn prevented the action of parathyroid hormone and its control of calcium in the birthing cow. The simple addition of chloride to feed would prevent the metabolic alkalosis and parathyroid blockade. Horst’s team would go on to make contributions to vitamin D metabolism and develop techniques for the assay of vitamin D and its metabolites.

In 1989, veterinary microbiologist Marcus Kehrli reported his discoveries of how white blood cells of the cow behave in mastitis. He found that hormones increasing during birthing suppressed bacteria-killing white blood cells and that this effect could be overcome by treatment with colony-stimulating factor, a cell-to-cell communication cytokine. As an offshoot of the study, Kehrli discovered a genetic defect, bovine leukocyte adhesion deficiency, coining the acronym BLAD. Holstein dairy cattle that were overly susceptible to bacterial diseases had a mutation in the gene that formed a critical protein that controlled the activity of these important circulating white blood cells. The gene defect made the cow unable to add surface receptors (called the β2 integrin adhesion molecules) to its white blood cell surfaces; the absence of these receptors on neutrophilic leukocytes made them unable to function as microbial-killing cells in the blood that are the first line of defense against bacterial disease. The BLAD gene was carried by many of the most-used sires and cows of the breed. Kehrli’s development of a diagnostic polymerase chain assay for detection of the BLAD gene solved a big problem for the Holstein cow.

American Sheep Industry Association: Eradicate viral pneumonia in sheep. Joining the National Animal Disease Laboratory after his graduation from veterinary school at The Ohio State University, Randall Curry Cutlip was inclined to sheep. He had been a sheep shearing champion—he had won shearing contests at the State Fair of West Virginia and the International Stock Show in Chicago—and was assigned to deal with respiratory diseases. For the next three decades he unraveled the mystery of how adenoviruses, parainfluenza viruses, and mycoplasmas cause acute pneumonia and the role that
superinfecting *Pasteurella* bacteria play in the sheep respiratory disease complex. It was a difficult task; sheep are notorious for masking signs of disease, often being “asymptomatic” when first ill.

Later in his career, Cutlip attacked ovine progressive pneumonia, a chronic and insidious respiratory disease caused by a new emerging group of retroviruses—called slow viruses or maedi/visna viruses—that infected 25 percent of North American sheep. Cutlip developed a definitive immunodiffusion diagnostic test for the disease. For his pioneering work, he was given an award from his alma mater and was named the Agricultural Research Service Scientist of the Year.

**National Cattlemen’s Beef Association: Develop a killed brucellosis vaccine.** The brucellosis eradication program for cattle was begun in 1934 by the USDA. The attenuated live vaccine, strain 19, was available and was responsible for the elimination of brucellosis in most of the states in the country. By the 1980s, the only remaining states that had bovine brucellosis were Oklahoma and Texas, and the only remaining focus of endemic bovine brucellosis caused by the bacterium *Brucella abortus* was the bison herds grazing in Yellowstone National Park. In the final mop-up of the disease there was a big problem with the strain 19 vaccine. Live bacteria in the vaccine caused vaccinated cattle to develop antibodies, making it impossible to determine whether a positive blood test had resulted from natural infection or from the vaccine. What was needed was a new vaccine, one that did not incite antibodies in the cow that would produce a misleading positive test that would be mistaken as a natural infection.

In 1986, under pressure from the National Cattlemen’s Association (NCA), Congress budgeted more than $60 million per year for five years directed to the eradication of brucellosis in cattle. Most of this would go to the field operations of the USDA’s APHIS; $10 million was designated for research at the Agricultural Research Service’s National Animal Disease Center, with two sub-grants of $1 million each mandated for universities in the two states that still had brucellosis in cattle: Texas A&M and Oklahoma State University. Annual meetings were to be held to present progress to APHIS and NCA that would justify funding.

In the annual meetings held in 1987 and 1988, all fund recipients failed to report significant progress. This caused progressively increasing criticism and condemnation of the NADC. The report of essentially no progress again in September of 1989 led to mandates for change. The NADC director was fired and
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