Pioneer Science and the Great Plagues

Cheville, Norman F

Published by Purdue University Press

Cheville, Norman F.

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

For additional information about this book
https://muse.jhu.edu/book/84018

For content related to this chapter
https://muse.jhu.edu/related_content?type=book&id=2892776
rapidly progressive cancer—a malignant T cell lymphoma that killed in thir-
teen to twenty-six days with massive invasion of body organs by malignant
lymphocytes. The malignant cells did not contain the virus, only the viral genes.

Veterinarian Ralph Brinster at the University of Pennsylvania was developing
new techniques for growing mouse embryos in cell culture and to manipulate
embryos to study embryonic cell differentiation. One of the most celebrated
veterinary scientists, Brinster founded a new discipline that dealt with transfer
of foreign genes into mammals, transgenic stem cell implants, in vitro fertiliza-
tion, and deletion of genes—knockout mice. He was elected to the National
Academy of Sciences in 1987 and received the Presidential Medal of Honor
from President Obama in 2010.

32. COMPARATIVE MEDICINE:
MODELS FOR LEUKEMIA

In 1908 two veterinarians, Vilhelm Ellermann and Olaf Bang, working at the
Royal Veterinary School in Copenhagen, published a report that proved what
field veterinarians had been telling them for some time, that avian leucosis—a
form of leukemia in chickens—was a transmissible disease. Their disciplined
experiments proved that to be true, and that whatever was causing the disease
was much too small to be a bacterium. At the time, the status of human leuke-
mia was vague; some physicians even suggested that human leukemia was not
a “true tumor.” No one in medical science took leukemia in chickens seriously.

Close on the heels of the Danes was a report in 1911 from the Rockefeller
Institute in New York City. Peyton Rous, also working with chickens, discovered
that a tumor composed of fibrous connective tissue—the Rous sarcoma—was
transmissible by a virus. No one in medicine thought much of that either. The
response of the scientific community to these seminal discoveries on virus-induced
cancers ranged from disinterest to disbelief.

To deal with continuing losses to the poultry industry from leukemia and
lymphoma, the Bureau of Animal Industry established a poultry research labo-
ratory in the 1930s in East Lansing—close to Michigan State University. The
big poultry problem was the avian leukosis complex, a group of lymphomas and
soft tissue tumors called big liver disease, range paralysis, and gray eye accord-
ing to the organ in which the lymphoma tumors grew in the sick birds. At
one end of the spectrum was avian leukemia, its viral nature established by the Danes in 1906; at the other end was Marek’s disease, a lymphoma first described by a Hungarian veterinarian in 1907. Marek’s disease became a serious problem in the 1950s when the industry moved to large crowded flocks grown in confinement. In 1967 the herpesvirus that caused Marek’s disease was discovered independently by Richard Witter at the Regional Poultry Laboratory and by English veterinarians. The virus was the only animal model for human lymphomas caused by the newly discovered Epstein-Barr herpesvirus. Witter followed the course of viral infection and showed that the Marek’s disease herpesvirus replicated to complete virus only in epithelium of the feather follicles of the skin and that as feathers grow, they shed infectious dander—the key to virus persistence and its elimination from chicken flocks. For his research, Witter was elected to the National Academy of Sciences.

Naturally occurring leukemia in mice was reported to be caused by a murine leukemia virus in 1951; in baby mice the virus first multiplied in the bone marrow and spread to the thymus to initiate the cancer in white blood cells. Soon there were large families of murine leukemia viruses, each named after their discoverer: Gross, Moloney, Rauscher, Friend, and others. The payoff day from the astonishing research in the 1930s on viruses that caused cancer arrived in the 1960s.

Leukemia was the hot topic for cancer research and spurred federal money to investigate animal models. Feline leukemia virus, the Rous sarcoma virus in chickens, the papilloma viruses in several animals, and the cancer-causing viruses of mice soon became universal models for cancer caused by viruses in the new field of viral oncogenesis. There were detractors. So many hypotheses were being tested in mice that one congressman referred to the National Cancer Institute as the “National Mouse Cancer Institute.” But by 1960, the older models of cancer in chickens to study human disease were resurrected. The importance of discoveries in the past was obvious when Peyton Rous of the Rockefeller Institute was awarded the Nobel Prize in 1966 for his discovery fifty-five years earlier of the Rous sarcoma virus in chickens (see appendix VI).

In 1964 a British veterinary pathologist reported in the journal *Nature* that a virus caused leukemia in cats. William Jarrett, working in the veterinary school in Glasgow, had been called by a practicing veterinarian, Henry
Pfaff, who had noticed a cluster of cats with lymphocytic leukemia. Suspecting a viral cause—it was a common disease in domestic cats—Jarrett successfully transmitted the cancer from one cat to several kittens. The cancer was contagious and could be passed horizontally—from cat to cat. Jarrett showed unequivocally that it was caused by a virus, feline leukemia virus. Astonishing electron microscopic photographs of feline leukemia virus by Jarrett’s colleague H. M. Laird published in the *Journal of the National Cancer Institute* four years later left no doubt that the virus was infecting cells of the cat. Their discovery was the coup de grâce for those who did not believe in viruses causing cancer.

The importance to human health was obvious, and federal funds from the National Institutes of Health for cancer research in animals were soon available to explore how viruses cause cancer. Financial support for comparative medicine was becoming available, and for the strongest programs easy to come by, especially if you had expertise in some field related to cancer.

**Bovine Leukemia Had Simmered** in the early 1960s as a public relations problem for the dairy industry; there was concern that milk-drinking children might be at risk. Leukemia was most prevalent in dairy cattle, whose individual health was more closely monitored than in beef cattle or other bovid species. The disease could be diagnosed early from blood samples by a massive increase in numbers of abnormal malignant lymphocytes, the white blood cells that in normal animals circulate in the bloodstream and are the source of immune reactions that protect against infectious agents.

In Europe, the Danes had led the way by their discovery of a clinically silent preleukemia phase of the disease—a slow but progressive elevation in the number of lymphocytes in circulating blood. On that basis, Denmark had started a program of screening dairy cattle for bovine leukosis and culling the cows that had this persistent elevation in lymphocytes. Hans Jørgen Bendixen, a veterinary officer of the Danish Veterinary Services, mapped the occurrence and incidence of bovine leukosis in Denmark—data that revealed the enzootic nature of the disease and led to his plan to remove affected cattle from the herds to eliminate it.

The crap hit the fan in 1967 when a medical virologist at the University of Pennsylvania, R. M. Dutcher, published what he believed to be leukemia virus particles in the milk of dairy cattle. He had examined milk from cows
with leukemia, but the particles he saw in the electron microscope could not be distinguished from amorphous particles of protein; they appeared to be residual milk proteins, not viruses. But that didn’t matter since the damage had been done—the press had played this out over all channels, dairy farmers were angry, politicians got involved, and funding was approved for bovine leukemia research. The U.S. Department of Agriculture’s Agricultural Research Service responded with major projects in four states.

At the University of Wisconsin, Carl Olson was an early recipient of some of those funds and showed that leukemia could be transmitted from sheep to cattle. A graduate student of Olson, Janice Miller, was the first to find the bovine leukemia virus. Artificially stimulating cell cultures of lymphocytes from the blood of cattle with persistent lymphocytosis, a preleukemia stage, she detected the virus using electron microscopy. Her results were quickly confirmed by scientists in California, Minnesota, and Nebraska, all of whom had received USDA grants to study bovine leukemia. Miller was elected to the National Academy of Sciences and spent the remainder of her productive career at the National Animal Disease Center (NADC) achieving credits for developing diagnostic tests for the identification of proteins of the agent of mad cow disease, bovine spongiform encephalopathy, and improvements in other diagnostic tests needed in animal diseases.

It was soon clear to science that BLV did not pass into commercial cow’s milk and presented no public health risk. However, American dairy associations saw it as a public relations problem that might affect the market and pressured the USDA to study how the virus behaved in cows. At the new NADC, a young veterinary virologist was hired to investigate how BLV infected milk cows and caused leukemia. Martin Van Der Maaten began growing cells in culture, inoculating them with white blood cells from a Holstein cow with preleukemic, persistent lymphocytosis; the cow was weak and emaciated and had generalized enlargement of lymph nodes. No BLV grew in the cultures. But the cultures were growing a new virus, one never before seen. Electron microscopy of the new virus revealed it to resemble visna virus, which had recently been reported from Iceland to cause a chronic, paralysis-inducing demyelination of the brain in sheep. Van Der Maaten called his new virus a “visna-like syncytia-producing virus.” When cattle were given the new virus, it caused persistent viral infection and generalized lymphadenopathy; no overt clinical disease resulted, and
studies of the new virus were abandoned. A decade later, the virus was named bovine immunodeficiency virus—BIV for short—the first retrovirus of its kind to be isolated, predating by a decade the identification of its close relative, the human immunodeficiency virus. When HIV was identified as the cause of AIDS, scientists at the National Institutes of Health remembered the Van Der Maaten paper and called for isolates of his original BIV.

Discovery of the virus that caused leukemia in cattle by Janice Miller at the University of Wisconsin was a major scientific event. The cover of the journal Cancer Research from February 1984 was dedicated to scientists who established the cause and behavior of the virus in cattle. Top (left to right): Hans Jørgen Bendixen, DVM, Denmark; Janice Miller, DVM, University of Wisconsin; Jorge F. Ferrer, MD, University of Pennsylvania. Bottom: Bendixen’s map of leukemia incidence in Denmark (left) and Miller’s electron micrograph of BLV (right). (COURTESY OF CANCER RESEARCH.)
In the larger progressive veterinary schools, scientific challenges of the new age were met head-on. Veterinary scientists at Ohio State, Cornell, and elsewhere soon clarified how the feline leukemia virus hides out in the cat and masquerades to cause not just cancer of lymphocytes but many different life-threatening changes.

At the Department of Veterinary Pathology at The Ohio State University, Professors Clarence Cole, Richard Griesemer, and Adalbert Koestner had set a high bar, creating the best in veterinary science. The productive research environment led directly to discoveries in the pathogenesis of leukemia viruses, but also in neurologic diseases of animals and in the complex relationships in calcium metabolism. The Ohio State veterinary school gave rise to Charles Capen, John Shadduck, and Thomas J. Rosol—all major leaders in pathobiological research and the advancement of veterinary science on the national level.

At Ohio State, veterinary pathologist Griesemer, in cooperation with virologists from the medical school, secured funding for the Special Virus Cancer Program to investigate the safety of newly emerging leukemia viruses in animals. Using their new facilities for germ-free technology—germ-free because the viruses were grown in tight isolation in bubble chambers and would not be exposed to external microorganisms—they discovered how feline leukemia virus developed in kittens. Veterinary pathologist Edward Hoover and colleagues showed that the FeLV affected the bone marrow, causing destruction of blood cell–forming stem cells. That led to studies on immunodeficiency and progressive white blood cell dysfunction, as well as an effective inactivated FeLV vaccine for cats. Hoover made career-long contributions to FeLV research, discovering viral proteins in circulating white blood cells. Throughout his career, he expanded on this discovery and made major contributions to how viruses cause cancer.

Turns out, FeLV was first multiplying in the bone marrow and then spreading to lymphoid tissues to cause leukemia, but its damage in bone marrow led to the suppression of many other stem cells—red cells that transport hemoglobin, neutrophilic white blood cells that are the first line of defense in bacterial infections, and monocyte, the white blood cells that mature into scavengers bearing “eat me” signals that gobble up bacteria and remnants of tissue damage. The clinical manifestations of the destruction of these different blood cells resulted in cats with life-threatening anemia, immunosuppression, and an inability to fight infectious disease. The similarity of the disease to that of humans made it a superior model for research.
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 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