APPENDIX VI

Animal Models of Cancer

Russian veterinarian Mstislav Novinsky reported in 1878 that he had successfully transplanted transmissible venereal tumors of the external genitals from one dog to another. Common in dogs worldwide, they grew on the penis and vulva and were transferred during mating. His discovery lay dormant for a century before this “one of a kind” tumor was shown to have originated from a precursor coyote, wolf, or ancient dog and to have survived in nature for over two thousand years as an allograft—not through passage of a causal organism, but as a self-perpetuating graft of tumor cells from one dog to another.

By the 1930s, comparative pathologists were revealing secrets about cancer. Of little interest to the public or to most physicians, the results were critical in our understanding of how cells become cancerous. Rabbit papilloma virus, the first mammalian DNA tumor virus, was reported by Richard Shope, an Iowan working at the Rockefeller Institute. Studying this endemic disease of wild cottontail rabbits in the Great Plains, Shope showed that the warty growths were transmitted through skin abrasions with infective debris.

At the University of Nebraska, Carl Olson had published his landmark studies on papilloma viruses as a cause of cancer: he had discovered that bovine papilloma virus, when infecting a superficial wound on the horse, did not cause papillomas but a common connective tissue tumor in the skin of the horse called equine sarcoid, a nasty fibrous tumor on the legs of the horse. Olson later reported that the same virus caused cancer in the bladder of cattle, and Scottish veterinarians reported that intestinal cancers in cattle could be produced by bovine papilloma virus. Decades later, medical virologists’ findings that papilloma viruses caused cancers of the human genital system were touted as incredible discoveries.

Cancer in animals was intriguing to scientists but not viewed as having much clinical importance. How cancer was caused was an enigma. As astonishing as it seems, the early studies on transmissible cancers in chickens, frogs, and rabbits
had been largely ignored by the public and generated an inappropriate lack of attention by most clinical oncologists. Scientists working in the large rodent colonies dedicated to experimental research had for years seen naturally occurring tumors in older mice. Mammary gland tumors were common in old female mice, and scientists began investigating the genetics of breast tumors and how they could be transmitted—by transplantation among hybrid mice.

In 1936, geneticist John Joseph Bittner, working at Jackson Memorial Laboratory, reported that a milk factor causing mammary tumors was transmitted in the mother’s milk: mice of low mammary tumor strains nursed by mothers of high cancer strains developed a high incidence of mammary tumors; conversely, mice of high cancer strains suckled by foster mothers of low cancer strains developed only a few tumors. These mammary tumors were discovered to be transmitted maternally and to have caused female offspring to develop mammary cancer. Bittner, born in Meadville, Pennsylvania, received a PhD from the University of Michigan with a thesis on the genetics of transplantation of breast tumors in hybrid mice. Working at the Jackson Laboratory where his milk factor research was done, he moved to the University of Minnesota for two decades before his death in 1961.

In 1939, Baldwin Lucké, a medical pathologist holding an appointment with Evan Stubbs in the veterinary school at the University of Pennsylvania, reported the first cancer-causing herpesvirus—the frog renal adenocarcinomas virus. This herpesvirus not only caused cancer of the kidney in leopard frogs, its life cycle involved a unique phenomenon in animals—temperature-dependent tumor growth. When virus from tumor-bearing frogs was released in the spring from the frog’s urine into the water, it infected newly developing frog eggs and tadpoles. Cancers then appeared in the third summer of the frog’s life, and many grew large enough to kill the frog. The “summer tumor” cancer cells did not produce virus but did contain the quiescent viral genetic material. If the frog was not killed by autumn, tumor growth stopped at hibernation. As the tumor cells ceased their growth cycles in cold weather, the latent herpesvirus genetic material was activated and the cells began to produce virus. The growing virus killed the tumor cells by lysis. But in spring, when hibernation ended, the virus was released into the urine and expelled into the pond water to begin the cycle again by infecting the new eggs and tadpoles.