# 100 years of Rous sarcoma virus

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**The discovery of Rous sarcoma virus, which was reported by Peyton Rous in the *Journal of Experimental Medicine* 100 years ago, opened the field of tumor virology. It showed that some cancers have infectious etiology, led to the discovery of oncogenes, and laid the foundation for the molecular mechanisms of carcinogenesis. Rous spent his entire research career at the Rockefeller Institute, and he was the *JEM*'s longest serving editor. Here, we comment briefly on the life of this remarkable scientist and on the importance of his discoveries.**

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This year marks the centenary of the publication in the *JEM* (Rous, 1911) of one of the twentieth century's most seminal discoveries in medical research, namely, the filterable agent that became known as Rous sarcoma virus (RSV). It earned the discoverer, F. Peyton Rous (1879–1970; Fig. 1) the Nobel Prize in 1966. Rous made his discovery at the Rockefeller Institute, as the University was then known, and he stayed there for the rest of his long and illustrious career. Why was the discovery important and why did it take so long for Rous to achieve the ultimate accolade of a Nobel Prize?

Peyton Rous was born on October 5, 1879. His father died when he was still a child, leaving his mother to raise three children on a meager income in Baltimore. As a youngster, Rous was fascinated by natural history. He studied at Johns Hopkins University, gaining his BA in 1900 and his MD in 1905. After brief periods investigating pathology at the University of Michigan and in Dresden, Germany, in 1909 he was invited by Simon Flexner to join the Rockefeller Institute in New York, where he worked for the rest of his life.

Rous's most famous discovery was finding that a sarcoma in the domestic fowl was transmissible to other fowl by a tumor extract that he had passed through a filter too fine to contain chicken cells or bacteria. In other words, the tumor-inducing agent was a "virus," which later became known as RSV. The importance of this finding was twofold. First, it demonstrated clearly for the first time that a malignant tumor could be induced by infection. Many other examples of tumor-inducing viruses in rabbits, mice, cats, and nonhuman primates eventually followed (Shope and Hurst, 1933; Bittner, 1942; Gross, 1951; Sweet and Hilleman, 1960), and the first oncogenic human virus, Epstein-Barr virus, was observed in 1964 (Epstein et al., 1964). Second, RSV represented a pioneering oncogenic retrovirus for investigating the molecular mechanisms of cancer development (Kurth and Bannert, 2010). Studies from

**Figure 1. Peyton Rous in 1923.** Reproduced with permission from the Rockefeller University archives. Van Epps, 2005. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.2013fta



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the late 1950s onwards, after a quantitative in vitro bioassay for RSV was devised by Temin and Rubin (1958), led to the identification of oncogenes, which were initially found in retroviruses (Toyoshima and Vogt, 1969; Duesberg and Vogt, 1970; Martin, 1970) and were later found in cells (Stehelin et al., 1976).

The *src* oncogene of RSV became the prototype for dozens of other transforming genes in oncogenic viruses. Oncogenes function in cell signaling from growth factors, and their receptors function through signal transduction pathways to nuclear transcription factors. For example, the *myc* gene was first identified in an avian myelocytoma virus and the *ras* gene was first identified in rat sarcoma virus long before they became associated with human malignancies. The *src* gene product was identified by Brugge and Erikson (1977), and it was the first protein to be shown to be a tyrosine kinase (Hunter and Sefton, 1980). These oncogenes provide a gain-of-function in cellular signaling, stimulating cell division and leading to malignant transformation. Not long after oncogenes were discovered, DNA tumor viruses were shown to encode proteins that sequester cell proteins and induce their loss-of-function for controlling the cell cycle. The genes encoding these cell proteins became known as tumor suppressor genes. An example is p53, a transcription factor of ~53 kD that was pulled down by immunoprecipitation of the polyoma virus SV40 protein large T (Lane and Crawford, 1979; Linzer and Levine, 1979). The binding of the large T protein to p53 leads to a loss of p53 transcriptional activity (Mietz et al., 1992).

The notion of transmissibility of tumors, however, predated Rous's discovery. In 1842, Domenico Rigoni-Stern observed that nuns in Verona rarely developed cervical cancer, compared to its frequency in married women (Scotto and Bailar, 1969), although the causative papilloma virus was not identified until 1983 (Dürst et al., 1983). Similarly, Jaagsiekte lung carcinoma in sheep was known to be transmissible in the nineteenth century, yet the causative agent, the Jaagsiekte retrovirus, was also only characterized in 1983 (Verwoerd et al., 1983).

The first filterable disease agent that we now classify as a retrovirus (lentivirus) was the equine infectious anemia virus (Vallée and Carré, 1904). In 1908, Ellerman and Bang (1908) of Denmark described a form of erythroleukemia in chickens that could be passed as a filterable agent. It represented the first example of an avian leukemia virus (ALV), but the malignant nature of leukemia was not generally recognized, and this important discovery did not have the impact of RSV. Even Rous's findings were not at first thought to be of particular interest because a solid tumor in a bird was not considered to be a suitable model for mammalian cancer. Viruses were thought to cause acute diseases that would rapidly appear in the majority of infected individuals. That paradigm was different from our modern knowledge of viral oncogenesis and of persistent infections with long latency periods.

When RSV was shown to contain an RNA genome (Crawford and Crawford, 1961), it became the prototype "RNA tumor virus," and after the discovery of reverse transcription (Baltimore, 1970; Temin and Mizutani, 1970), the term "retrovirus" came into use. 60 years after the discovery of RSV, the first retroviral infection in a human was reported (Achong et al, 1971). This was a foamy virus that we now know represented a primary zoonotic infection from a chimpanzee, and it is apparent that primate foamy retroviruses frequently infect exposed humans (Switzer et al, 2004). It was not until 1980 that human T cell leukemia virus type I (HTLV-1) was found to be the first genuine human retrovirus with oncogenic properties (Poiesz et al, 1980) causally associated with adult T cell lymphoma-leukemia (Yoshida et al., 1982). We currently know of four circulating human retroviruses (HTLV-1 and -2 and HIV-1 and -2); there have also been many false alarms (Voisset et al., 2008), the most recent of which was the apparent link of a xenotropic murine-related retrovirus to human prostate cancer and to chronic fatigue syndrome ( Cohen and Enserink, 2011).

Today, we tend to regard retroviral infections as being ubiquitous among vertebrate species. While this may be the case with endogenous retroviral genomes that are transmitted as Mendelian genes in the host (Kurth and Bannert, 2010), not all well-studied species harbor known retroviral pathogens. It is curious that no infectious retroviruses have been identified in dogs, whereas cats harbor leukemia viruses, immunodeficiency viruses, and foamy viruses. The most recently discovered oncogenic retrovirus is the infectious leukemia virus of the koala, a virus that is undergoing a process of endogenization (Tarlinton et al., 2006).

It is interesting to return to the step by step progress of Rous's research. Rous (1910) became interested in the transplantability of tumors when a woman came to the Rockefeller Institute with a Plymouth Barred Rock hen with a large tumor (Fig. 2). At that time, highly inbred mice were not yet available, although Loeb (1901) had started to experiment on tumor transplantation with a sarcoma in a partially inbred line of white rats. The canine transmissible venereal sarcoma (Novinski,1876) was the only tumor to be naturally

**Figure 2. The original Plymouth Barred Rock fowl bearing the tumor presented to Rous and held by somewhat arthritic hands.** Reproduced from Rous, 1910.

or experimentally transplantable across major histocompatibility barriers, even to foxes, but not by a filtrate (Sticker 1906). Rous cites this transmissible venereal tumor of dogs, referred to as "Sticker's lymphosarcoma," in his 1910 paper, but it took an additional 100 years to firmly establish that the transmissible agent of the canine tumor is not a virus at all, but is actually the tumor cell itself (Murgia et al 2006).

Rous (1910) wrote: "In this paper is reported the first avian tumor that has proved transplantable to other individuals. It is a spindle-celled sarcoma of a hen, which has thus far has been propagated to the fourth generation. This was accomplished by the use of fowls of pure blood from the small, intimately related stock in which the growth occurred. Market bought fowls of the same variety have shown themselves insusceptible, as have fowls of mixed breed, pigeons and guinea-pigs."

Some months later, however, Rous found that the tumor had greatly increased its transmissibility in chickens, and that was when he successfully tested a cell-free filtrate (Rous, 1911). We can do no more than speculate with the hindsight of our greater knowledge of avian retroviruses why the filtrate did not take in diverse strains of chicken straight away. If the original strain of RSV was replication defective, requiring a complementing ALV for propagation, then a different ALV strain in one of the birds through which it was passed may have provided the expansion of host range. Alternatively, the original tumor might have had an activated cellular *src* gene that only became incorporated into an ALV genome de novo during experimental passage.

Rous subsequently reported the isolation of two other transmissible avian tumors (Rous and Murphy 1914), as did Fujinami and Inamoto (1914) in Japan. Thus, the observation of an oncogenic chicken virus was not a one-off phenomenon. Rous dropped the investigation of avian tumors at the onset of the First World War, when he became involved in pioneering work on blood transfusion and helped to establish the first blood banks in the USA. He did not return to his avian tumor work after the war; he may have been discouraged by the lack of recognition of the discovery of RSV as an important one. However, Rous did maintain an interest in oncogenic viruses, and in the 1930s he encouraged his Rockefeller colleague, Richard Shope, to study the skin papillomas of rabbits. Soon after Shope's description of rabbit papilloma virus (Shope and Hurst, 1933), Rous embarked on a series of studies lasting nearly 30 years, in which he used the benign viral papillomas as a precursor to malignant tumors induced with chemical carcinogens (Rous and Beard 1935; Rous and Kidd, 1940; Rous et al., 1952). He was the first to conceptualize carcinogenesis as occurring in two distinct stages, initiation and progression, although it was Berenblum and Shubik (1947) who showed how effective nonmutagenic phorbol esters are in inducing tumor progression.

Curiously, Rous eschewed the idea that somatic mutation was an essential route to cancer development (Rous, 1959), and he stubbornly held onto his view that cancer is not a genetic disease in his Nobel lecture (Rous, 1967), which was delivered 3 years before his death at the age of 90. Even the greatest scientists can have blind spots! Despite his beliefs, his discovery of viruses containing oncogenes and his studies of mutagenic chemical carcinogens are now seen as laying the foundation for our understanding of the multiple somatic genetic changes that occur in malignancy, as revealed by complete sequencing of cancer cell genomes (Stratton, 2011).

In addition to his own research, Rous became the longest serving editor of the *JEM*, fulfilling this duty from 1922 until shortly before his death in 1970. In 1946, René Dubos joined him as an assistant editor. Dubos (1979) has said that Rous selected him for this duty after a lunchtime discussion on whether medicine was a science or an art. Dubos expressed the view that at the Rockefeller Institute all that mattered was that researcher have a "hunger for facts." This enthusiasm for evidence-based medicine, as we now call it, epitomized Rous's own attitude to research. As an editor, Rous championed clarity above elegance and preferred good plain English to long words of Latin origin.

Peyton Rous had to wait 55 years for his discovery to be recognized by the honor of a Nobel Prize, which is the longest "incubation period" in the 110 years history of the Nobel Prizes in Physiology or Medicine. One reason for this delay may have been that the immense importance of

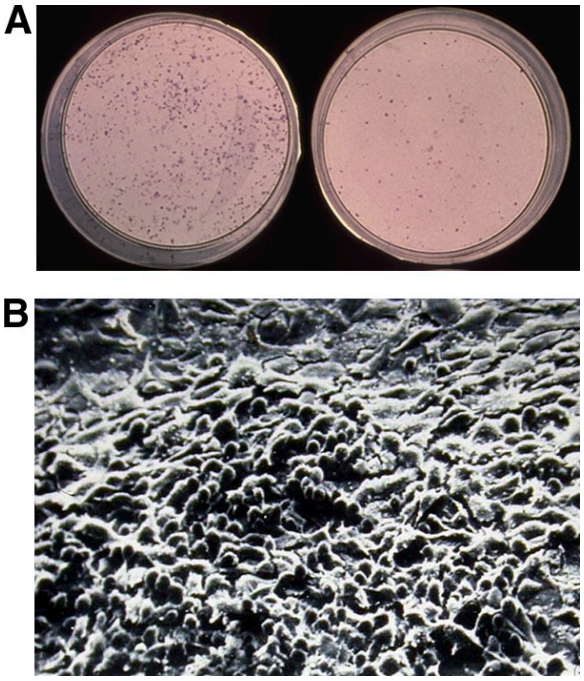


**Figure 3. Cell transformation by RSV.** (A) The RSV focus assay of transformed cells in a chick embryo fibroblast monolayer as described by Temin and Rubin (1958) showing a 1:100 and 1:1000 dilution of the virus stock. Each stained dot represents a focus of transformed cells. (B) A scanning electron micrograph of one focus of RSV-transformed cells. It was the ability to transform cells in culture and to isolate individual clones of RSV that led to the molecular biology and genetic studies of tumor viruses. (Reproduced from Weiss, R.A., PhD thesis, University of London. 1969.)

his discovery was not evident until the 1960s, when a renaissance of RSV studies occurred thanks to the virus's ability to transform cells in culture (Temin and Rubin, 1958; Fig. 3). But according to Norrby (2011), Rous was nominated on several occasions from 1929 onwards. Another reason for hesitation may have been the fact that the Nobel Committee had burnt its fingers with the award to the Danish physician, Johannes Fibiger, in 1926 for his discovery of an apparently oncogenic parasite in rats that later turned out to have no association with the tumor. In the aftermath of Fibiger's Prize, the Nobel Committee may have been overly cautious, and no further Nobel Prizes in the field of cancer were awarded for 40 years until Rous was recognized alongside Charles Huggins, who had discovered the therapeutic role of steroid hormones in controlling certain cancers.

Times and attitudes have changed. RSV has earned later investigators two more Nobel Prizes: Howard M. Temin and David Baltimore in 1975, for the discovery of reverse transcriptase (Temin and Mizutani, 1970; Baltimore 1970), and Harold E. Varmus and J. Michael Bishop in 1989, for the discovery of the cellular origin of the retroviral oncogenes exemplified by *src* (Stehelin et al, 1976). The Nobel Prize in Physiology or Medicine of 1976 went to Baruch Blumberg for the discovery of hepatitis B virus, a causative agent of hepatocellular carcinoma (London et al., 1969). Moreover, three novel infectious agents in humans that have a cancer association were each discovered in 1983—a vintage year for pathogen discovery (Weiss, 2008)—which led to Nobel recognition: Barry Marshall and Robin Warren in 2005 for their discovery of *Helicobacter pylori* (Marshall and Warren, 1984), and in 2008, jointly, Harald zur Hausen for identifying cervical human papilloma viruses (Dürst et al., 1983) and Françoise Barré-Sinoussi and Luc Montagnier for isolating HIV (Barré-Sinoussi et al., 2004). Today, we appreciate that ~20% of the global burden of human cancer has an infectious etiology (Parkin, 2006) for which preventive measures such as vaccines have great promise. Peyton Rous's meticulous investigations on viral cancer, reported in the *JEM* 100 years ago, have had a mighty legacy indeed.

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