Peyton Rous was awarded the Nobel Prize in 1966, when he was eighty-six years old, for discoveries he had made fifty years before. He was born on the 5th of October 1879 in Baltimore, Maryland, to a family that valued humanistic education. Thus, after the death of his father, when Peyton Rous was a child, his mother rejected the idea of joining her family in Texas and stayed in Baltimore, where excellent education for the children was available. Of the two sisters of Peyton Rous, one became a musicologist, the other a painter; and Peyton himself had a flair for writing.

Peyton Rous enrolled in the Medical School of the recently created Johns Hopkins University, which he attended without special distinction. As an undergraduate he showed a naturalist's tendency and published articles about Baltimore's flowers. After graduating in medicine, he went to the University of Michigan, where he began his research career in pathology, which he perfected during a year in Dresden. In 1909 he joined the Rockefeller Institute under Simon Flexner, to engage in cancer research, against the opinion of influential friends who thought it was a hopeless field. There he remained until his death. In 1921 he became co-editor (and later editor) of the Journal for Experimental Medicine. In 1927 he was elected to the National Academy of Sciences. He died in 1970, at the age of ninety, and
is survived by his wife, Marion, and three daughters, Marion, Ellen, and Phoebe.

In addition to the Nobel Prize, Peyton Rous received many honors and honorary degrees, which are listed at the end of this memoir.

The name of Peyton Rous became widely known to biologists in the fifties and sixties for his earlier discovery of a virus causing sarcoma in chickens, which became aptly known as the Rous Sarcoma Virus. At the time he became famous, Peyton Rous appeared as an elderly, highly educated, gentleman with silvery hair. But in his youth he was a very hardworking scientist with a determined, fiery, and highly critical personality. He was a medical man who wished to learn about cancer as a disease and a biologist who did not want to follow the beaten track, and he was willing to hunt for new clues in well-designed but slow experiments.

I, like most of my contemporaries, became acquainted with Peyton Rous’s fundamental discovery in the early fifties, when Harry Rubin came to my lab to work with the Rous Sarcoma Virus. He started using a focus technique on the chorioallantoic membrane of the chicken embryo, which Rous had invented many years before. Later I had occasion to meet Peyton Rous several times on the platform as a speaker, or across the discussion table, or in his laboratory at the (then) Rockefeller Institute. I remember the man—rather small in stature with silvery hair and penetrating eyes. I also remember that before our first meeting I was inclined to think of him as a figure of the past, but soon changed my mind at that meeting and even more so at subsequent ones. Clearly, he was very much alive until his very last days, with a keen interest in new developments in virology and cancer research. He was able to discuss his past work with equanimity and to accept new interpretations of his data. I remember I suggested to him an explanation of the clonal characteristic of the neoplastic transformation of papillomas in terms
of somatic cell genetics, a concept that was not part of cancer research in the period of his active work. His interest was immediately aroused; he asked me for a thorough clarification of what I meant and then argued, with passion but no animosity. We parted like old friends who have found something new to talk about. At the time when phage lysogeny was the domain of a very small group of virologists, I suggested to him that it might represent a good model for some features of viral cancer. Again his interest was acute, and I had to embark on a detailed discussion of phage integration, immunity, and lysogenic conversion.

Peyton Rous discovered the viral etiology of a chicken sarcoma in 1911 through his interest in tumor transplantability to new hosts by a filtrate. He commented: "The behaviour of the new growth has been throughout that of a true neoplasm, for which reason the fact of its transmission by means of a cell-free filtrate assumes exceptional importance" (1911).

He fully realized from the outset that this was "a unique and significant finding" (1911). He also realized that the significance of the discovery depended on the true nature of the induced growth. As an experienced pathologist he could see that it was a true cancer: "The (pathological) picture (of the growth) does not in the least suggest a granuloma... it exhibits to a special degree, not merely a few, but all those features by which the malignant neoplasms are characterized" (1911).

For about forty years this momentous discovery had little impact, because the minds of scientists were not prepared to think of viruses as agents of cancer. It was expedient to say that the chicken tumor was not a cancer, but some kind of reaction to the virus more akin to inflammation than neoplasia, and perhaps a peculiarity of chicken biology. Peyton Rous soon recognized himself that the tumor would not be accepted as a cancer because it was transmitted by a cell-free extract: "A passing reference should perhaps be made to the ill-defined
group of pathological products called granulomata, with which this neoplasm of the fowl may by some be classed, owing to its transmission by an agent separable from the tissue cells” (1911). Many years later he wrote, “This disclosure (that certain chicken tumors were proved due to viruses), which conflicted with the negative findings in mammalian growths, was determined forthwith as erroneous” (1952).

One wonders how firmly in the early years Peyton Rous himself was convinced that he had demonstrated the induction of a cancer by viruses. The statements he made at the time are very cautious and full of qualifications. At first he used to refer to the “agent” that induced the sarcoma; but a year later, after he discovered a new, different tumor transmissible by filtrate, he proposed that the “agent is probably a living virus” (1912).

During the years 1911–1914, Peyton Rous worked hard at disproving the objections on the nature of the induced tumors by isolating other viruses that induced tumors in chickens and by carefully studying their pathology. He could show that the tumors induced by the different viruses were capable of invading neighboring tissues and of metastasizing to distant organs; thus they were true cancers. Moreover, each independently isolated virus caused a tumor of a different kind. These facts should have been convincing evidence that the growths were specific responses of the host, yet this conclusion was not generally accepted. However, these discoveries seem to have been convincing for Rous, who wrote, “The findings with the chicken tumors largely demolish the theoretical basis in which objections to an extrinsic cause for cancer have been built up” (1912).

In order to find more generally acceptable evidence, Peyton Rous attempted to extend his observations “especially through carefully devised experiments with the tumors of other species of animals” (1911). Evidently for the viral etiology to be accepted, similar findings were needed in mammals. The strategy of Rous’s future work was determined at that time. However,
the extension to other species came only many years later with Richard Shope's discovery of the rabbit papilloma virus.

In the meantime Peyton Rous studied many features of the cell-free transmission of the tumor. Examining the effect of the age of the host, he showed that the virus induces characteristic foci on the chorioallantoic membrane of the chicken embryo. This result supplied an assay for the virus that was universally employed until the fifties, when it was superseded by the focus formation in tissue culture.

In this extensive and careful work, Peyton Rous observed the host resistance to the transmission of the tumor, in the form of either absence of growth, slow growth, or normal growth followed by regression. Other experiments showed how essential the conditions of the host are for the development of a tumor after inoculation of the virus. From this observation Peyton Rous began to recognize the existence of limitations to the expression of the oncogenic potential of the virus: "How does it happen that the sarcoma, though ultimately dependent on an extrinsic agent, is dominated in its behaviour by the cells composing it?" (1912). Perhaps the agent depends "on a special set of conditions in order that it might produce a neoplastic change" (1912). He returned later to this point on several occasions.

After discovering the second chicken tumor agent, Peyton Rous started wondering about the etiology of cancer in general: "The demonstration that extrinsic agents are the cause of two connective-tissue growths of the fowl which are characteristic malignant tumors renders it necessary to suppose either that such tumors of the fowl have an entirely different etiology from mammalian tumors, or else that the latter are of similar origin" (1912). This point was also developed to a much greater extent later on.

As further evidence for a viral nature of the chicken tumors, the resistance of the host to the tumor cells could be separated
from its resistance to the tumor-inducing agent. Moreover, Rous discovered a third chicken tumor, transmissible by filtrate, markedly different in properties from the two previously described: "The findings with the three tumor-producing agents have a striking similarity and it is difficult to avoid the conclusion that the three are of one class, whatever that class may be. . . . It is perhaps not too much to say that their recognition points to the existence of a new group of entities which cause in chickens neoplasms of diverse characters" (1914).

At the beginning of World War I, Peyton Rous, under the pressure of wartime medical needs, gave up his work with chicken tumor viruses. For the following twenty years until 1934, his interest was in the fields of blood transfusion and attending immune reactions, liver and biliary functions, cellular functions, and vascular permeability. I will return to these activities later on.

A turning point in Peyton Rous's work on cancer was the discovery of the Shope papilloma. In 1933 Richard Shope reported his discovery that a mammalian tumor, the papilloma of cottontail rabbits, was transmitted by a virus-like agent. As in the case of the chicken tumor, Peyton Rous's first concern was whether the papilloma was a true neoplasm. He decided that it was, because, when the papillomas were transplanted deep inside the body, they developed into carcinomas that grew invasively and killed the host. Furthermore, in domestic rabbits the virus-induced papillomas often grew progressively, invading the neighboring tissues and producing metastases, and this malignant evolution could be enhanced by exposing the papillomas to various substances, such as Scarlet Red.

These findings seem to have been for Rous the decisive argument for the validity of his conclusions concerning the chicken tumors, since in a mammal cancer could also be transmitted by a virus. He, therefore, returned to the study of carcinogenesis using the papilloma virus as a new tool. He focused
at first on the malignant evolution of the papillomas. By careful
observations, following small hints, such as the shape of their
growths, color, or the degree of pigmentation, he showed that a
few cells in a papilloma became cancerous and generated clones,
each with different characteristics.

In trying to understand how such evolution to cancer occurs,
Peyton Rous studied the effects of tar, as both a carcinogen and
tumor promoter. He found that tar not only strongly enhanced
the induction of papillomas or carcinomas by the Shope virus
in domestic rabbits but by itself elicited similar papillomas.
Could tar papillomas also be virus-induced?

This new phase of Peyton Rous's work, although a natural
development of his earlier work, had more ambitious goals, for
it aimed at testing the hypothesis that "this disease (cancer) is
an infection. . . . A main attraction of this hypothesis is its
accessibility to test." However, he clearly saw that this hypothe-
sis could only be true under certain conditions, one of which is
that "a living entity responsible for such growths must require
for effectiveness a very special basis of predisposition" (1932).
He sought to possibly disprove the infectious nature of cancer
by comparing the frequency of cancer induction by tar in the
skin of two groups of mice with different exposure to the envi-
ronment: "The animals of one group have been placed under
conditions which would facilitate the entrance into the body of
extraneous living agents, whereas those of the others have been
sedulously protected" (1932). The results proved "that the mouse
cancer cannot be caused by living entities reaching the body
from the surrounding world during adult life" but "fail to
exclude the possible activity of entities residing habitually in
or upon the body" (1932). This experiment showed another re-
quirement of the hypothesis on the infectious nature of cancer:
"The supposition (that tumors in general are due to viruses or
other extraneous entities) is tenable only if such entities are
widely distributed throughout the animal population, being
constantly present in or upon the body, like the colon bacillus or the staphylococcus; and if their opportunity to cause tumors is restricted by the need for very special conditions. . . . The more considerable an agent is conditioned in its activity, the more often must it be present if it is to cause disease at all” (1934). These words were prophetic, as shown by the recent developments in the field; yet they were simply the result of cool, logical assessment of the facts then in hand. However, for Peyton Rous this hypothesis was only a guide for the experiment: “The demonstration of the cause for the generality of tumors, whatever this is, awaits upon the provision by the investigator of the conditions necessary to its effectiveness” (1934).

He tried several new approaches. One of the major tools was still the technique of inducing skin tumors by application of tar. He used it to create favorable cellular conditions for revealing the neoplastic potential of viral agents. Another tool was the immunity of the infected rabbits against the Shope virus. Peyton Rous found no demonstrable antibodies in rabbits without papillomas or in those with tar papillomas or Brown–Pierce tumors: these findings “speak decisively against the possibility that these growths are caused by viruses antigenically related to the one causing papillomas. Yet this does not exclude a virus causation for them, since the sera of fowls with Chicken Tumor I and Fujinami Sarcoma respectively, though possessed of neutralizing power for the virus causing the growth carried by the host, have no cross-neutralizing effect whatsoever” (1936).

Shortly afterwards, in taking a bird’s eye view of his past work and of the cancer problem, he concluded: “How far should one be led by the assumption that certain tumors may be due to viruses? Only so far as to make tests with these growths. The tumor problem has withstood the most corrosive reasoning. Yet since what one thinks determines what one does in cancer research, as in all else, it is as well to think something. And it may prove worthwhile to think that one or more tumors of
unknown causes are due to viruses” (1936). He thus recognized that the problem that he so clearly formulated and actively pursued eluded experimental attack and remained unsolved. In fact he later restated the basic question: “What is the papilloma doing in the cancer, if anything?” (1940).

In a renewed effort to answer this question, Peyton Rous used as a new tool the famous line of transplantable rabbit cancers, derived from a viral papilloma called at first “carcinoma V2” (1940), and then, after World War II, V × 2 because during the war V2 “came to have another significance” (1952). This line did not contain infectious papilloma virus, but for many serial transfers in rabbit it continued to elicit the production of virus-specific antibody.

The result suggested that the virus may play a determining role although in “masked or altered form” (1940). This was a new idea in virology, which had enormous developments many years later. For the next three years, during serial transplantation from one rabbit to another, the V × 2 carcinoma continued to elicit this immune response. However, when it was retested after an interval of one and a half years, four and a half years after its origin, the tumor was found unable to immunize against the papilloma virus; the loss of this property “was not attended by any perceptible change in the V × 2 carcinoma” (1952). This “wholly unexpected” result must have been quite shattering; and Peyton Rous was led to rethink the role of the virus in the production of the cancer. In this agonizing reappraisal he proposed that the virus might have undergone “wider variation” (1952); but he recognized that “at this uncertain point the problem of the cause for the V × 2 carcinoma must perforce be left” (1952). In this way the work of Peyton Rous went full circle: from complete ignorance on the role of viruses in cancer to definitely establishing such a role through brilliant discoveries, to postulating a wider and possibly general role of viruses in spontaneous cancers, and ending up again in
a condition of uncertainty. I should not say full circle, but rather one turn of the helix, because the uncertainty was now of a different kind.

The emphasis of Peyton Rous’s work in the forties and fifties shifted from the viruses to chemical carcinogens. Many articles were dedicated to the potentiating effect of tar and other carcinogens on virus-induced papillomas. During this work it also became clear that tar alone induces papillomas very similar to those induced by the virus on normal skin or on skin pretreated by tar. In all cases the growth showed progression, i.e., remained benign for some time and then developed into carcinomas, which arose in a few isolated cells. However, many observations also showed that the role of the virus and of the chemicals was different: “The generality of the carcinogens bring about tissue conditions out of which tumors may or may not arise for reasons still undetermined. They may be fitly called provocative carcinogens. The viruses, on the other hand, both initiate tumors and determine their character and behaviour. They are actuating carcinogens” (1943).

In a new series of experiments, Peyton Rous convincingly demonstrated that the viral and the chemical agents have a cooperative action, producing in combination cancers at much higher frequency and after shorter time than either agent alone. On the basis of this cooperation, Peyton Rous made three important suggestions. One bears on the mechanism of carcinogenesis. He proposed that in utero or at a young age the human or animal body becomes invaded by viruses that “would give no sign of their presence in most instances. . . . But if a provocative carcinogen happened to work on the cells with which such a virus was associated . . . it might undergo variation and . . . give rise to a tumor. The new pathogenic variant would not be transmitted to other animals . . . but would be a dead-end virus, though the harmless source virus liable to the same or other variation would be passed on” (1943). This hypothesis is very
similar to some prevalent at the time of this writing, if the
dead-end variant is interpreted as a defective integrated provirus
that has incorporated a silent oncogene, causing its expression.

Another suggestion was that chemical carcinogens might
cause the so-called spontaneous tumors. He added, "A list of
human tumors which have been traced to the action of provoc-
tive carcinogens is in no small degree a sociological document,
reflecting as it does the ways of life, vocation, avocations, habits
and environmental stresses of people and individuals" (1943).

The third suggestion was that viruses and chemicals in combi-
nation might have a continued role in spontaneous cancer:
"The recent discovery that viruses of some sorts lie latent for
long periods, causing disease only on special occasion, coupled
with the realization that some tumors have viruses as their cause,
has led to a supposition already mentioned that agents of this
sort may reside in animal tissues, perhaps throughout the life-
time of the organism, doing no harm unless the cells with which
they are associated undergo special pathological changes, when
they undergo variation as a result of the new, abnormal milieu
and render the cells neoplastic. According to this supposition,
tar and methylcholanthrene are carcinogens because they alter
the environment of viruses. . . ." (1944). Such a possibility is
very much in the minds of virologists and oncologists today.

During his work on carcinogenic hydrocarbons, Peyton Rous
identified important features of the neoplastic process they
initiate. One is that their cancer-inducing activity is greatly
enhanced by promoters that stimulate cell proliferation, for
instance, wounds. Another feature is that "cancers arise by a
step-like progression" (1941). Peyton Rous recognized the im-
portance of this observation, because "the cells of not a few
tumors attain to their worst by further neoplastic changes which
are scarcely less significant than the one primarily responsible
for their state. Indeed the practical significance of these changes
is often greater as meaning death to the patient" (1955).
In his later years Peyton Rous continued his experimental work, but his contributions declined in number and relevance. During that time tremendous changes were occurring in biology, especially the great development of genetics and the birth of molecular biology. Although Peyton Rous showed great interest in these developments, he failed to assimilate them. Obviously, even a brilliant mind is subject to the limitations of age. He became attached to old concepts. The main consequence was his rejection of somatic mutations as a possible cause of cancer and his failure to recognize viruses as new genetic material in the cells they infect. It may be said about him what he said about Leo Loeb: “He outlived his era of discoveries about cancer but what he did for science endures” (1960).

The work on cancer is the big basis on which Peyton Rous’s fame rests. The other work, which I already mentioned, is permeated by a similar perceptiveness, imagination, and experimental ability. I should mention especially the work on blood preservation and substitutes, which Peyton Rous carried out during World War I, because it shows another facet of his personality, i.e., the ability to respond to urgent medical needs of society. For instance, in 1918 he wrote: “There exists at present a great and urgent need for an injection fluid that can be satisfactorily employed instead of blood for transfusion in cases of hemorrhage. It is common knowledge that casualty clearing stations, after a ‘push’, are crowded with men who have lost too much blood to be operated on, who cannot be revived by means of salt solutions and supportive measures, but who would undoubtedly respond to transfusion. For the latter neither time nor donors are available.” Quite rapidly, at the beginning of the war, Peyton Rous and associates perfected a method for storing human red blood cells, using a weak gelatin solution to protect them during washing and sugars to preserve them. The procedure was used to establish the first blood bank
during the war, which was operated by one of Rous's collaborators. And the solution for suspending the red cells, known as the Rous–Turner solution, is still in use. Such an accomplishment would be a sufficient reason for fame, because it has both scientific and humane values. We know that Peyton Rous was very proud of it.

In addition to his experimental work, Peyton Rous had another absorbing interest: the editorship of the Journal of Experimental Medicine. It is known that he dedicated to it an immense amount of time and energy. He was reputed for the accuracy of his editing, both in regard to scientific content and style. I well remember when I, as a prospective author, first encountered him as an editor. He returned my manuscript with many remarks, mostly of style. I remember I was at first baffled, but then, after studying his comments further, came to appreciate their reasons, which went beyond the mere words. I realized that for him a word, every word, was a concept, which should be examined not only in its present, but also future, context. He reminded me in his letter that I should think that a certain word might become widely adopted and that I should therefore choose it with deliberate care. He was anticipating the flooding of scientific literature with laboratory slang, which has happened in recent times and which was a trend of which he strongly disapproved. But during his editorship, he succeeded in maintaining the Journal of Experimental Medicine at a high level, both in purity of language and strength of content.

Peyton Rous remains in the minds of those who knew him, especially the younger generation, as the image of a man fully dedicated to his work, a scientist with vision, a strong although kind person, with a good sense of humor. His experiments were always designed to test hypotheses and developed in a logical sequence on the basis of results already secured; they were very methodical and thorough and were reported in detail with ex-
treme clarity. He was independent in thought and was against conventional beliefs unsubstantiated by evidence. For instance, he commented:

"Not so long ago in the dark ages of medicine, one could think nearly anything about disease because one knew almost nothing. Theoretical system succeeded system, from humours to homeopathy. Opinions strongly held appeared like realities and were acted upon as such. Now for most diseases all this is at an end: fact has killed fancy. . . . The tumor problem is the last stronghold of metaphysics in medicine" (1936).

Although during his career he formulated some penetrating hypotheses not amenable to direct test, he was fundamentally interested in facts: "No explanation of the cause of cancer is worthy of attention that cannot be tested" (1932).

The language of his reports was vivid, full of images from everyday life, as shown by a few examples:

"The fowl limps and its wings seem stiff" (1913).

"The growth gives it (the fowl) a factitious plumpness" (1913).

"During the outward extension of the membrane (of the Kupffer cells), lava-like flows can be seen on its surface, when the light is cut down, and at its edges fimbriated or 'petaloid' extrusions, at times appearing whip-like, which are in constant slow motion" (1934).

Comparing his work with the chicken viruses, which started with a cancer and led to a virus, and with the Shope virus, which started with a virus and led to a cancer: "The trails have met at the same look-out. What does one see from this?" (1936).

His humor was sometimes biting: Speaking of new reactions elicited in the human body by surgery, he saw their positive aspects: "All that surgery has done in such instances is to make plain the relation of effect to cause, as for example in showing that tetanus is due to insufficiency of the parathyroids, and myoxedema to a thyroid lack" (1929).
The most visible side of Peyton Rous was his interest in scientific truth, in the younger people, the equanimity of judgment and the warmth of human relations he was able to establish both inside his family and outside. I had a hint of this when recently his daughter, Marion, referred to him as "daddy" in an affectionate way; and when several years ago he wrote to me sending his congratulations for the Ehrlich Darmstaedter award (which he nominated me for) and suggesting the nicest Ratskeller in Frankfurt, with the best food, wine, and atmosphere.

Peyton Rous received many official honors in his life, including the highest. But the paramount recognition was the admiration and respect of his younger colleagues, which continues after his death.
HONORS AND DISTINCTIONS

Honorary degrees from the universities of Cambridge, Michigan, Yale, Birmingham, McGill, Chicago, and Zurich
Member of the National Academy of Sciences
Member of the American Philosophical Society
Foreign Member of the Royal Society
Member of the Royal Danish Academy of Sciences
National Medal of Science
Cleveland Medal of the American Cancer Society
Gold-headed cane of the Association of Pathologists and Bacteriologists
United Nations Prize
Gold Medal of the Royal Society of Medicine
Albert Lasker Award
Landsteiner Award of the American Society of Blood Banks
Distinguished Service Award of the American Cancer Society
Kovalenko Award of the National Academy of Sciences
Ehrlich Darmstaedter Prize
Kober Medal of the Association of American Physicians
Benter Medal and Award of the University of Texas
Walker Prize of the Royal College of Surgeons
John Scott Medal and Award of the City of Philadelphia
Nobel Prize for Medicine (shared with Charles Huggins)


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1910


1911


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1918


1919


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