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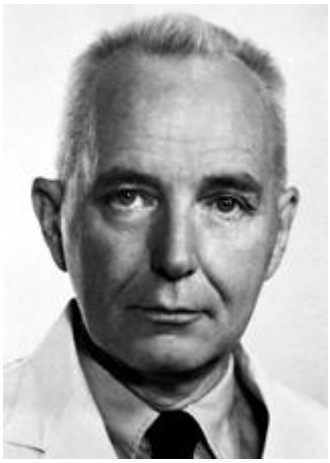
Nobel Prize in Medicines 1966

Peyton Rous



Charles Brenton Huggins

The Nobel Prize in Physiology or Medicine 1966 was divided equally between Peyton Rous "for his discovery of tumour-inducing viruses" and Charles Brenton Huggins "for his discoveries concerning hormonal treatment of prostatic cancer"

The year was 1910. Only recently had it been understood that every cell of the body has been derived from another cell by division and that cancer cells divide in approximately the same fashion as normal cells, differing only in their tendency to invade recklessly normal tissue barriers; and only very recently had it been realized that some infectious diseases were due to organisms which are invisible even in the light microscope and are capable of passing through the pores of an ultrafilter, impenetrable for bacteria. They were designated as filterable «poisons» or viruses. At or around this time, with some outlines of the enormous edifice that was to become modern biology barely in sight, no relationship could be conceived to exist between the invisible viruses and the self-sufficient growth of cancer cells.

Around this time, Peyton Rous, 30-year-old research worker at the Rockefeller Institute, carried out some experiments that may have appeared farfetched at first sight. He

prepared cell-free filtrates from a malignant connective tissue tumour - a sarcoma - that appeared spontaneously in a hen and inoculated it on healthy chickens. Surprisingly enough, the recipients developed tumours of the same type as seen in the original animal. The disease-causing agent present in the filtrate, known nowadays as the Rous sarcoma virus No. 1, could be propagated by serial passage through chickens or fertilized eggs.

Stimulated by this successful experiment, Rous continued his work and showed that even other hen tumours, originating from such tissues as bone, cartilage or blood vessels, could be transmitted by cell-free filtrates. It was remarkable that after inoculation every filtrate reproduced its own original tumour type with great fidelity.

Soon after Rous' discoveries, many research workers tried to transmit mouse and rat tumours in a similar way. The results were negative. In most research workers' minds, this has led to the conclusion that the chicken tumours of Rous represented some curious exceptions, unable to contribute to the understanding of tumour causation in mammals.

In 1932, Shope discovered that a benign skin tumour (papilloma) in a wild cottontail rabbit could also be transmitted by cell-free extracts. Rous became interested and could soon show that while these tumours were originally quite restricted in their growth and tended to regress and disappear spontaneously after a certain period, they could also change to malignant cancers under certain conditions, particularly after exposure to small and by themselves inefficient quantities of chemical cancer-inducing agents.

In connection with these experiments Rous conceived for the first time that the change of normal cells to cancer cells was not necessarily sudden; unlike Pallas Athena who emerged from the head of Zeus with complete armour, subordinated cells of the body could develop into independent, anarchistic cancer cells through several, stepwise changes. In the beginning of this process, designated by Rous as «tumour progression», the potential cancer cells are in a «dormant» state. Chemical agents, viruses or hormonal stimulation may awaken them to a more aggressive life.

Rous' findings concerning tumour progression were rapidly confirmed in many experimental systems. On the other hand, his virus theory was received with much

skepticism. The notion that virus diseases must be infectious and cancer not due to infectious processes was so deeply ingrained that there was a tendency to explain all virus tumours as strange exceptions. The Rous sarcomas were regarded as bird tumours, of no importance for mammals; the Shope papilloma was a mammalian tumour but of benign nature; and when Bittner discovered in the 1930's a milk-transmitted virus causing breast cancer in mice, it was generally believed that this virus was of minor importance, in comparison with the genetic and hormonal factors that were known to play a rôle in the genesis of this particular tumour.

The situation changed radically in the 1950's. The study of tumour viruses is a central area of modern cancer research. Two developments are responsible for this remarkable change. Recent developments in microbial genetics have lead to reinterpretation of the virus concept itself. It turns out that certain types of virus can introduce parts of their own genetic material into a cell without killing it or inhibiting its multiplication. The virus material thus introduced may become actually integrated with the gene material of the recipient cell and behave as a new hereditary factor. Virus infection can thus lead to a permanent change in some cellular characteristics. This re-evaluation of the virus concept made it possible to understand how a tumour virus might change the regulated behaviour of normal cells to the malignant proliferation characteristic of cancer cells. In the same period many new viruses capable of inducing malignant tumours in mammals were discovered. In 1981 Gross found a virus that induces leukemia in mice. A few years later he and two women scientists, Stewart and Eddy, isolated a remarkable new virus, called polyoma, capable of inducing an array of tumours in many different mammalian species. Since 1960 more than a dozen new tumour virus types have been isolated. It was established, furthermore, that tumour viruses could change normal to cancer cells in the test tube after a very short time of contact. This opened the way for direct studies on cancerous transformation of human cells, an approach previously hidden behind the walls of the living organism. Remarkably enough, it could be shown that Rous' own virus, previously regarded as lacking any importance for mammals, induces cancer

under certain conditions in many different mammalian species and may even transform human cells in test tube cultures. Swedish scientists in Lund and Uppsala have made important contributions in this regard. It is not yet clear in which way viruses induce cancer but there is much to indicate that the virus does not behave like a little boy setting fire to a hayrick and running away; part of the viruses' own genetic material seems to be directly responsible for the malignant behaviour of the virus transformed tumour cell.

It took almost half a century for Rous' discovery to advance to its dominant place in modern experimental cancer research. In contrast, the discovery of Charles Huggins was of immediate practical applicability and has already given many valuable and relatively symptom-free years to gravely ill cancer patients throughout the civilized world. At first glance, the contributions of Rous and Huggins may appear as of entirely different nature. They have, however, a common denominator. Both were concerned with the question: Is the cancer cell completely self-sufficient and independent of all normal regulating mechanisms of the organism, or does it still maintain some of the responsiveness of the normal cell? Rous showed that there are some tumour cells that do not grow by their inner tendencies but rather due to the outside influence of virus or chemical agents. Huggins found that other tumour cells could show a similar dependence towards certain natural hormones of the body. He started to study the normal prostatic gland in dogs and found that its function and growth were stimulated by male sex hormones and inhibited by female sex hormones. This was the starting point for the hormone therapy of human prostatic cancer, based on the assumption that the human prostate may react to hormones essentially in the same way as the dog prostate, and that cancer cells of the prostate may retain part of the hormonal responsiveness of the normal cell. This reasoning suggested treatment by eliminating the male sex hormones through castration, and/or antagonizing them by introducing female sex hormones.

Remarkably good therapeutic results were obtained, showing that the basic assumptions were correct. More than one-half of patients with advanced prostatic cancer, already beyond a stage accessible to surgical therapy, due to cancerous invasion of

neighbouring normal tissues, or even metastases to distant organs, showed an objective reduction in size, or disappearance of the tumours, including those which had spread to other organs. These patients who would not have had more than a short time to live without this treatment, became frequently free of symptoms for many years. This was a completely new type of cancer therapy, capable of helping a previously unaccessible category of patients, by the administration of non-toxic, naturally occurring hormones rather than by toxic or radioactive agents, and with few side effects.

In addition to the therapy for prostatic cancer Huggins has also introduced the hormonal treatment of human breast cancer. The clinical value of this treatment is more limited, due to the fact that breast cancer cells have often lost the hormone responsiveness of their normal ancestor cell. Even this treatment has given symptomatic relief and long tolerable periods to otherwise incurable patients.

Surprisingly enough, Peyton Rous was among the first to recognize the importance of Huggins' discovery. He wrote that «... the importance of this discovery far transcends its practical implications; for it means that thought and endeavor in cancer research have been misdirected in consequence of the belief that tumor cells are anarchic».

No one else has clarified the causes and limitations of this anarchy better than Rous and Huggins.

Dear Dr. Rous. You have discovered the first virus that induces solid tumours in animals and have thereby opened the field dealing with viruses and cancer, - a field so important for the understanding not only of tumour causation, but also of the change whereby normal cells turn into cancer cells; - a change, the nature of which you have done so much to elucidate.

Dear Dr. Huggins. Your fundamental discoveries concerning the hormone dependence of normal and neoplastic cells in experimental animals and their immediate practical application to the treatment of human prostatic and breast cancer have already given many years of an active and useful life to patients with advanced cancer over the entire civilized world; - patients who would have been lost to all other forms of therapy.

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Dr. Rous and Dr. Huggins. Your studies meet in the central question just how anarchistic cancer really is. While both of you have shown that tumour cells may go, to use your terminology, Dr. Rous, from bad to worse, you have also found that they are not always as bad as they could have been.

It is a great pleasure and honour for me to express the congratulations and admiration of Karolinska Institutet and ask you to receive the Nobel Prize from the hands of His Majesty the King.

For more details please visit:

http://www.nobelprize.org/nobel_prizes/medicine/laureates/1966/press.html