

## Perspective

# The role of viruses in the etiology of cancer and leukemia in animals and in humans

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Contributed by Ludwik Gross, February 28, 1997

In the first half of the current century, the etiology of malignant tumors was fully ignored, without any serious attempts of clarification. In general, cancer and leukemia were thought to be caused by “somatic mutation,” whatever this term means or represents.

There were several observations, however, that did not conform to such a concept: chicken lymphomatosis, chicken sarcoma, and frog kidney carcinoma could be transmitted from one animal to another within the same species by cell-free filtered extracts; mammary carcinoma in mice could be transmitted from mothers to daughters by milk (reviewed in ref. 1). Mouse leukemia was thought to be of “genetic” origin and not transmissible by filtrates, until we demonstrated in 1951 that mouse leukemia is caused by a filterable RNA virus, which causes leukemia and lymphomas, following inoculation into *newborn* mice (2) or rats (3). Following serial passage, the potency of this virus could be substantially increased, comparable to Pasteur’s “fixed virus” of rabies in dogs.

Under natural life conditions, the mouse leukemia virus is transmitted from one generation to another, through the embryos (4). However, the incidence of disease in successive generations does not follow the Mendelian inheritance laws.

### Radiation-Induced Leukemia

In further experiments we demonstrated that radiation-induced leukemia in mice is not of “genetic” origin, but is the result of activation, by ionizing radiation, of a dormant virus (5). We isolated this virus and passed it subsequently by serial mouse-to-mouse passages (6).

Following these important observations, viruses were found to be the etiological factors causing leukemia or tumors in a variety of animal species, such as cats (7), monkeys (ref. 1, chapters 23 and 28), and cattle (ref. 1, chapter 21). It was also realized that the same virus can induce (i) tumors or leukemia (ref. 1, chapters 23 and 28), (ii) inflammatory disease (8), or (iii) no disease at all.

Thus, infection with a potentially tumor-inducing—i.e., oncogenic—virus does not necessarily lead to the development of a neoplastic disease. Very frequently, no disease is induced at all. Occasionally, however, tumors may develop in the carrier hosts when the pathogenic property of the virus is triggered by a variety of chemical or physical factors.

### Transmission of Cancer by Inoculation

Cancer and leukemia are not transmissible from person to person, except, and this exception is of great importance, among genetically related family members. Inoculation of humans with live human cancer extracts of *close relatives* such as mother to daughter or son, or among brothers and sisters,

etc. may lead to the establishment of progressively growing tumors in recipients and cause dissemination of a fatal disease (9). On the other hand, the result of inoculation of cancer extracts from human patients to unrelated human recipients are unpredictable. In rare instances, the implanted tumors may “take,” grow progressively, and lead to a generalization of the disease. Administration of immunosuppressive drugs, such as azathioprine or prednisone, lowers natural resistance of the host to heterologous tumors; patients receiving such treatment are particularly susceptible to transmission of human cancer.

### Attempts to Prevent Development of Cancer

Very often we hear or read about suggestions referring to *procedures aiming at prevention of development of cancer*; these suggestions refer to men or women of certain age and assume that all these individuals are equally susceptible to the development of cancer. Such an assumption, however, is incorrect. We are not equally susceptible to the development of tumors. If cancer is caused by a virus transmitted from one generation to another, as we assume at least as a working hypothesis based on experimental studies of cancer in many animal species, it would then follow that individuals with a family record of cancer in current, or one or two preceding, generations are more prone to develop this disease than those that have a negative family record for this disease.

As a typical example, let us refer to *breast cancer*. A. Lacassagne from France received a United Nations Prize for his studies on the induction of breast cancer in male mice, following injection of estrogenic hormone; the injected mice were of an inbred line in which females develop mammary carcinomas spontaneously. However, the same dose of estrogenic hormone inoculated into male mice of another inbred line in which females, as well as males, remain free from spontaneous development of this disease did not induce such tumors in the injected males.

This brief example demonstrates clearly that *we cannot treat a general population as equally susceptible to cancer, but have to treat differently those that have a family cancer record*, as compared with individuals having a healthy family history, free of this disease.

The same refers to *mammography*. Recently recommendations were made suggesting that all women should have mammograms at age 40 to detect early development of breast cancer. Again, in this example women who have a family history of breast cancer are more likely to develop this disease than those that have a negative family history for breast cancer. We have to take into consideration, however, that breast cancer, or other malignant tumors, might have developed in the negative group two or three generations ago, which may not be known to those now alive; for that reason, this negative group should also be submitted to tests and mammography, but perhaps with less urgency and lower expectations of positive results.

### Moderate Reduction of Food Intake May Reduce the Incidence of Tumors

Among the preventive factors in the course of developing malignant tumors and lymphomas is the *influence of food intake*. Recent studies demonstrated that in mice and rats at least, and presumably also in humans, moderate reduction of food intake may considerably reduce the incidence of radiation-induced or spontaneously developing tumors or leukemias (10).

### A Working Hypothesis

The majority of tumors and leukemias in a variety of animal species has already been demonstrated to be caused by transmissible agents belonging essentially to the world of viruses. Would we, the humans, belong to a different, special, group different from the rest of the world of living species?

Current, apparently generally accepted, theories of cancer origin mention "genetic factors" which have different names, and are considered to be transmissible or acquired (?) in certain families or individuals. Are such genetic factors the real cause, or do they suggest only that some viral agents might have left their implants on genetic components of the nuclear DNA? Let us have an open mind. Let us accept and comprehend the devastating role that the invisible and transmissible viruses can play in our lives, and let us try to understand their biology, transmissibility, and in some instances dangerous effects on our lives.

It is true that thus far, human tumors have not been transmitted by filtrates to animals, and that, except in rare instances, no virus particles have been found on electron-microscopic examination of human tumors or leukemias. However, we cannot assume on this basis that human cancer is not caused by oncogenic viruses. Let us remember that mouse leukemia was considered for several decades to be a nonviral genetic disease until it was transmitted by inoculation of filtered extracts into newborn mice. Similarly, bovine lymphosarcomas could not be transmitted to calves or to other species until by accident, it was discovered that *bovine leukemia could be successfully transmitted to newborn lambs* (ref. 1, chapter 21).

Electron-microscopic examination of tumors known to be of viral origin does not always reveal the presence of virus particles. Very frequently virus particles are detected only under specific experimental conditions—for example, *after passage in tissue culture*, or by examination of susceptible virus-infected organs *before the development of tumors*.

In summary, experimental evidence is now available demonstrating that the great majority of malignant tumors, as well as leukemias and lymphomas, in animals is caused by transmissible, oncogenic viruses. These viruses are widely disseminated in a variety of animal species and most probably also in human beings; usually they are frugal and moderate in their requirements, causing in most instances no harm to their carrier hosts. However, when triggered by a variety of metabolic, hormonal, or chemical factors or by ionizing radiation, they may become pathogenic and cause the development of malignant tumors or leukemia in their hosts.

### Tentative Conclusions

Oncogenic viruses probably represent a very old, latent infection that has been transmitted from one generation to another for many centuries; they have remained in most instances submerged, invisible, and unrecognized, except for an occasional cancer or leukemia developing in one of their carrier hosts. Although no clear experimental evidence is yet available of a viral etiology of human tumors and leukemias, it is only reasonable to assume that neoplastic diseases can be caused by viruses not only in animals but also in humans.

We must also realize that in most instances the potentially oncogenic viruses live in relative harmony with their carrier hosts, and are transmitted peacefully from one generation of their carrier hosts to another. Induction of an ultimately fatal disease of their hosts due to an accidental activation of the oncogenic potency of the virus, prompted by a variety of internal or external factors, ultimately destroys not only their carrier host but also the virus. Fortunately these are only occasional and relatively rare circumstances. In most instances the viruses are and have been transmitted peacefully for many centuries from one generation to another, on and on, causing no apparent harm to their carrier hosts. This is similar to many other diseases transmitted "vertically," from one generation to another, in animals and in plants.

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