

Viruses and Carcinogenesis

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The disease process, now known as cancer, has been recognized at least since the Egyptians of the 15th century, B.C.; and the public dread of it ensured a ready supply of theories of causation throughout the years. Since Galen in 550 A.D., who attributed cancer to the accumulation of "black bile", there have been innumerable hypotheses, most of which have been figments of fertile imaginations and few of which had any rational scientific backing.

Descartes postulated a lymphatic etiology, and started the vogue of humeral hypotheses, that were accepted until pathology turned its attention away from body fluids and concentrated upon cells. A rash of new and wild speculations followed this trend in pathology. For instance Mallion felt that Cupid held the key to carcinogenesis in suggesting that sexual contact between a cell of the fixed tissues and a migratory leucocyte or a microbe started a cancer. In Hallion's own words: "By this anarchistic act, the cell is freed of all control over its further development. The harmonious plan followed until then, could hardly be more expressly violated than by an inopportune and unanticipated fertilization that substitutes for the normal growth impulse—a generative impulse entirely new. The guilty cell gives rise to a free race that recalls both in habit and origin those species in which the cells pursue an independent existence". This idea, although of considerable moral interest, was soon cast aside with many other less picturesque theories. Now we are left with basically three theories of causation:

1. The Irritation Theory—including all physical and chemical agents that have been observed to cause neoplastic growth.
2. The Embryonal Hypothesis.
3. The Infective Theory—involving microbes, parasites and viruses.

This paper intends to explore the latter theory, and present the postulated modes of action of the viral etiology of carcinogenesis.

A little background history is perhaps in order: Variot and Jadassohn in 1894 and 1896 are credited with the first transmission of tumor from man to man. They used the common wart and were able to inoculate it from person to person. It is noteworthy here that this occurred before the existence of viruses was actually realized.

Sanarelli in 1898 transmitted myxomatosis in rabbits with a cell free filtrate, and Ciuffi used this method in 1907, and set the stage for the well known experiments of Rous in 1911, and the less well known experiments of Ellerman and Bang in 1908—all using chickens. Rous was able to transmit an extremely malignant sarcoma from fowl to fowl with a cell free filtrate. He postulated two mechanisms, but adhered to neither—first he suggested the transmission of what he called a "minute parasitic organism", and second he suggested the possibility of transmission of a chemical stimulant elaborated by the neoplastic cells. His main emphasis, however, was less with the transmissibility of the tumor, than with the dependence of successful transmission upon the character and condition of the individual host. However, his imaginative series of experiments aroused little scientific enthusiasm, and the work was dropped with the onset of the First World War; and he did not take it up again for twenty years or more. By this time the intellectual climate was changed, and other tumor inducing viruses had been discovered.

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Shope in 1932 demonstrated the viral etiology of rabbit fibromata and papillomata, and in so doing helped generate the vast amount of research into this whole subject that is increasing up to the present time.

Now more than thirty different viruses that can initiate animal cancer have been reported. Bittner in 1936 discovered the mammary cancer virus of mice, Gross in 1951 discovered leukemia viruses in mice, Stewart in 1957 isolated the polyoma virus and its carcinogenic potentialities. Trentin in 1962 correlated adenovirus 12 and 13 with tumors in hamsters. Di Mayorca and his associates in 1959 showed that polyoma virus DNA itself could initiate tumors, Ito reproduced this work with Shope papilloma DNA and Moloney (1962) showed that RNA of mouse leukemia virus also has oncogenic powers.

The list of such achievements is long, and hardly bears repeating in its completeness at present.

Thus, viruses have been found that cause solid tumors or leukemia in many animals, in fact many people maintain that all fowl and all mouse tumors are virus induced. So far all attempts to apply this work to man have failed. In two instances, actually, viruses have been recovered from human tumors, but in experimental situations, these viruses failed to reproduce tumors. Again, the injection of human tumor extracts into mice has raised the incidence of tumors in the mice—however, it was felt that this was due to activation of inherent mouse viruses rather than a direct function of the human tumor tissue itself. Thus, to date, there has been no unequivocal proof of the viral etiology of any human malignant tumors.

It may well be that the methods of study in the animal field are not applicable to man, and it is the basic understanding of how viruses change normal cells into malignant ones that will provide a more logical attack to this experimental problem. For this reason, I will centre this paper on the proposed mechanisms of viral carcinogenesis.

It is generally considered that viruses have a direct action on cells, rather than an indirect action on the whole animal that predisposes or facilitates neoplastic transformation by mechanism other than viral. It has been shown experimentally that another carcinogenic agent—X-ray—can act indirectly—as proven by the transplant and subsequent malignancy of normal thymic cells in an irradiated animal. This, however, is not true of viral carcinogenesis, as experimental evidence indicates that both the Rous sarcoma virus and the polyoma virus will act on cells growing in vitro, and will induce what is presumed to be malignant change. It thus appears that the virus can act oncogenically upon cells directly. This is of particular interest, as no other postulated carcinogen, neither chemical nor physical, has been made to produce such a change in vitro, in other words, no other carcinogen has such strong evidence of its direct action in carcinogenesis.

Once direct action is assumed correct, three possibilities of mechanism present themselves and can be illustrated in the following models:

1. The virus may be present in the cytoplasm of cells, multiply within them, and by its mere presence induce an increase in mitosis, leading to malignancy. In this situation, the genetic make up of the affected cells is not changed and the malignant nature is dependent upon the presence of virus multiplying within the cells.

2. The virus may penetrate to the nucleus of the cell, and become associated with its genetic materials, the virus losing its intact nature as it does so. Thereafter, as the cell reproduces, the nucleic acid of the virus is reproduced also, as part of the cell genetic material. Thus the cell's genetic information is altered, and provides the potential for malignant growth.

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3. Again the virus enters the cell nucleus, however, in this case the genetic information is changed by subtraction rather than addition. The virus injures the genetic material without actually becoming associated with it; and after the injury plays no further part in the action of the cell. The lesion in the genetic makeup is permanent, however, and leads either directly to malignancy, or may only predispose the cell to further mutations leading ultimately to malignant change.

Experimental evidence of the possible validity of these models does exist—thus in the Rous sarcoma experiments it was found that once a group of cells have been transformed to malignancy, then the virus is virtually always found in the cells, in fact malignant cells have been seen to go through mitosis, and the daughter cells continue to excrete viruses. Thus this type of malignancy conforms to the first proposed model. However it should be pointed out that although this indicates that the presence of virus is definitely compatible with continued cell proliferation, it does not conclusively prove that the virus is essential for the malignant nature of the sarcoma cells.

In contradistinction to the Rous sarcoma virus, the polyoma T virus seems to have two distinctly different effects on the invaded hamster cells. This is shown by the difference in histological picture four to seven days after injection of the virus, and that ten days after injection. In the former instance there are numerous necrotic cells containing intracytoplasmic and intranuclear inclusion bodies, as well as the numerous mitotic figures of the mesenchymal cells. These latter are not noted to have any inclusion bodies. At this stage, viruses are easily isolated from the tumor. By the tenth day, no necrotic cells remain, only the proliferating tumor cells. In these cells no virus can be seen as inclusion bodies, nor can viruses be demonstrated by any known method of bioassay. Thus in this instance, carcinogenesis seems to be consistent with either the second or third model—that is either the incorporation of viral material in the genetic make up of the cell, or alteration material, without the virus being actually incorporated.

If any tumor in man were analagous to the Rous sarcoma, it would be reasonable to assume that a causative virus might be found—as it would presumably be contained in the tumor cells. Demonstrating the fact that such a virus is the causative agent, however, presents a considerable problem, as it is hardly acceptable to attempt to reproduce the tumor in a newborn child—as would be the case in an animal experiment.

If models two or three were involved in mans' cancer, then the proof of the possibility of viral etiology comes even more difficult, as tumor cells here are free of the complete virus. Even in the case of the second model, wherein the viral material is represented in the genetic make up of the cell, animal experiments have so far failed to help in providing methods of demonstrating the presence of viral interference.

Ludwik Gross has a working hypothesis on the viral etiology of cancer that fits well with animal experiments, and ties together many seemingly unassociated facts. He feels that an oncogenic virus may be infectious only in the vertical scale, not the horizontal, that is the virus is handed from generation to generation, through either the germinal cells, or through the mother's milk (as in mouse breast cancer virus). Gross then postulates that an activating influence is needed to stimulate the virus to produce neoplasia. These activators he feels may be external—for instance, ionizing radiation; or may be internal—for instance hormonal influences. Whether or not a person harboring such a virus actually develops cancer, even in the presence of such activation, may depend upon the factors that condition the host—either increasing its susceptibility to activation of the latent oncogenic virus. For instance—famine inhibits the activation of the virus, as does the presence of specific antibodies to latent virus.

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With such a hypothesis, it follows that the development of a tumor or leukemia would only occur in a minority of those actually carrying the potential for the disease. Verification of this model is possible in animals, as many generations may be bred in a relatively short time, and the vertical transmission of virus proven. This, however, is not possible in man, due to the vast time that would be involved.

In 1944 Dr. Charles Oberling said that the only major disadvantage of the virus hypothesis was that "it has not been proved". In 1964 few can doubt the viral etiology of many animal cancers, but unfortunately Dr. Oberling's statement still holds true for the cancers of man.

The future for the research in this field must be regarded as one of the most important and thought provoking in the whole of medical research. Experimental transmission, tissue culture techniques and electron microscopy offer the obvious and perhaps most valuable methods of continuing research. However, epidemiology may provide considerable help.

At present, however, we can only speculate, and I feel that Oberling may have come close to the truth when he remarked that "some day, perhaps, it will turn out to be one of the ironies of nature that cancer, responsible for so many deaths, should be so indissolubly connected with life itself".

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