Do Viruses Cause Cancer in Man?

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Many factors are involved in the induction of animal and human cancer: ionizing radiation, chemical carcinogens, age, hormone balance and genetic constitution of the host. In addition, viruses are known to cause tumors in animals such as frogs, fowl, rodents, cats, cows and monkeys, and it is improbable that cancer in man has a fundamentally different etiology.

However, it is unlikely that evidence of the viral etiology of human cancer will ever fully satisfy Koch’s postulates. These include that: (1) the micro-organism must be observed in most cases of the disease; (2) it must be isolated and grown in pure culture; (3) the pure culture must, when inoculated into a susceptible animal, reproduce the disease; and (4) the micro-organism must be observed in, and recovered from, the experimentally diseased animal. Thus, supporting evidence that viruses cause several human cancers is largely circumstantial and has been gathered in several ways. One line of attack is to search for virus particles, viral precursors in the form of antigens, and virus-specific nucleic acids in human tumor biopsy samples and cultured tumor cells. Passenger and contaminant viruses should be rigorously eliminated before any agent can be considered oncogenic. Another approach is to experimentally induce tumors by inoculation of human tumor material or putative human oncogenic viruses. Resulting animal tumors are then examined for candidate human viruses. One drawback of this method is that animal viruses may also be picked up during the experiment, complicating the results. A recent example is the isolation of putative human oncornavirus from tumors in cats following inoculation with human rhabdomyosarcoma cells. Unfortunately, subsequent work proved that the virus was of animal, not human, origin.

Data on the viral etiology of human cancer have also been accumulated by monitoring the ability of a virus to transform cells in culture. Evidence of oncogenic transformation includes: the capability to grow indefinitely in culture; the loss of contact inhibition; the alteration of surface properties; and frequently, the capacity to induce tumors. That a number of human viruses can transform cells in vitro suggests oncogenic potential.

In addition, seroepidemiological surveys of human populations are attempting to correlate the presence of anti-virus antibody, indicative of previous viral exposure, with tumor incidence. The findings have associated Epstein-Barr herpesvirus with Burkitt’s lymphoma, and herpes simplex virus type 2 with cervical cancer. Epidemiological studies on the incidence of clustering in human cancer are also

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To date, four groups of viruses have been found to cause cancer in animals. Despite extensive study, there is no evidence that the papovaviruses and adenoviruses—DNA viruses which induce solid tumors in rodents—can cause tumors in their natural hosts, including man. A possible exception is a human papovavirus, or group of papovaviruses, isolated from the central nervous tissue of patients with progressive multifocal leukoencephalopathy. This disease frequently occurs in individuals with immunosuppressive disorders (e.g., Hodgkin's disease) and histologically resembles malignant glioblastoma. Furthermore, virus isolated from these patients can induce brain tumors in newborn hamsters. Whether the virus is able, under certain circumstances, to express the same malignant potential in man remains to be seen.

Two groups of viruses have been consistently associated with naturally occurring cancer: oncornaviruses containing single-stranded RNA, and herpesviruses composed of double-stranded DNA. The DNA viruses can become integrated into the host chromosome directly, but the oncornaviruses need the enzyme, reverse transcriptase.

ONCORNAVIRUSES

Characteristics

The oncornaviruses, or RNA tumor viruses, resemble one another structurally, chemically and physically, but differ in the target cells they transform and type of tumor produced. Also they can be serologically classified as: (1) type specific—antigenic determinants that differentiate between various viral strains in one animal species; (2) species specific—antigenic determinants that are similar in all or almost all virus strains of a given species; and (3) interspecies specific—antigenic determinants that cross-react broadly with the corresponding viral antigens in animals of the same class but another species. A human virus is expected to be more closely related antigenically to primate viruses than to avian or feline viruses.

The most important characteristic of oncornaviruses is that they contain DNA polymerase. This enzyme, in effect, reverses the usual direction of information (DNA → RNA) so that DNA is produced on a RNA template. This DNA intermediate is then integrated into the host genome, causing neoplastic transformation by some unknown mechanism. (Fig. 1.) In enzyme assays the initial DNA product is complexed to the RNA genome; these complexes can be detected by their position in cesium sulphate or glycerol gradients and by polyacrylamide gel electrophoresis. RNA tumor viruses do not normally destroy their host cell; indeed, multiplication of both virus and infected cell can proceed with or without cell transformation, depending on the particular virus strain.

C-Type Viruses and Animal Cancer

A category of oncornaviruses, the C-type viruses, has been isolated from many animal species and primarily implicated in sarcomas and leukemia. Since these cancers are most common in young patients, the value of studying sarcoma/leukemia model systems should not be underestimated. Virus C-type particles observed in animal sarcomas are very similar to those found in leukemia cells; both are about 100 nm. in diameter and contain RNA of molecular weight $10^7$ daltons.

Three groups of animal oncornavirus have been identified: (1) leukemia viruses which do not transform cells in vitro; (2) sarcoma viruses which are usually defective, transform cells in vitro and can produce infectious progeny only in the presence of a "helper" virus (Fig. 2); and (3) endogenous
RNA tumor viruses which are vertically transmitted and probably non-pathological in their natural host.

Based on experiments using inbred mice, tumor induction has been ascribed to the activation of repressed endogenous oncornaviruses by physical, chemical or biological carcinogens. There is some doubt, however, whether this mechanism is important in outbred animals under natural conditions; avian and feline leukemia viruses are apparently transmitted horizontally. It is probable that the etiology of cancer in man is similar to that in outbred animals. Confirming data are provided by two cases in which leukocytes from monozygous twins with leukemia contained oncornavirus-like nucleic acid that was not detectable in the healthy child. If the oncornavirus were vertically transmitted, it would be present in cells of both twins. Unfortunately no strong epidemiological evidence as yet suggests that a horizontally transmitted virus is involved in human leukemia.
C-Type Viruses and Leukemia in Man

Human C-type oncornaviruses have not yet been definitively identified, although several characteristic components have been found in human acute leukemia cells. An enzyme closely resembling typical oncornavirus reverse transcriptase has been purified from leukemia cells. This enzyme is inhibited by antibody to reverse transcriptase from primate tumor cells, but not by antibody to avian or feline leukemia virus reverse transcriptase, nor to human DNA polymerase. There is also evidence for oncornavirus nucleic acid in human leukemia cells, which has sequences in common with mouse and, particularly, monkey oncornavirus nucleic acid. Similarly, certain antigens associated with the murine and primate oncornaviruses have been recently detected in many human neoplasias. However, interpretation of these observations is difficult since similar antigens are being detected in "normal" human tissues.
Virus-like particles have been identified in human leukemia cells, but as they are defective and not normally released, their role in neoplasia is obscure. A human leukemia oncornavirus is suggested by viral “footprints” found in cells from 22 of 23 leukemic patients, but not in normal or abnormal non-malignant leukocytes. Confirmation of these results would provide fairly good evidence for a human leukemia virus.

Unequivocal proof of a human C-type virus, whether or not associated with cancer, would greatly facilitate the search for related human viruses; serological and genetic investigations could then be carried out under far more stringent conditions than are possible in cross-species comparisons. That this may be soon realized is strengthened by two very recent reports which claim to have isolated human type C viruses.3,4

**Fig. 3. Comparison of mouse mammary tumor virus and particles from human mammary tumors.**

**B-Type Virus and Mouse Mammary Tumors**

B-type RNA virus, associated primarily with certain tumors of the breast, is serologically distinct from C-type viruses and has a characteristic appearance under the electron microscope. Like the C-type viruses, however, it contains single-stranded RNA and multiplies via a DNA intermediate synthesized by the virion reverse transcriptase.

The archetype B-particle satisfies Koch’s postulates as the etiologic agent of mouse mammary adenocarcinoma. The virus is transmitted in milk as well as in seminal fluid and gametes. Virus genetic material that is vertically transmitted is integrated into the host chromosome and is present in every cell of the adult mouse. The expression of virus functions, however, presumably depends on the appropriate environmental conditions that are found in
mouse breast tissue. Tumor incidence in different strains of mice varies widely, and the importance of genetic and hormonal factors in determining disease occurrence is well established. It is believed that these factors control the expression of the virus' oncogenic potential and hence tumor growth.

**B-Type Particles and Human Breast Cancer**

Breast tissue and milk from healthy and tumor-bearing women have been examined under the electron microscope for virus-like particles, and extensive epidemiological surveys have tried to determine whether breast cancer has an infectious etiology. Particles resembling mouse mammary tumor virus have been found in milk samples, but only rarely. (Fig. 3.) Rather more easily demonstrated is the presence of high molecular weight RNA and an oncorna-virus-like reverse transcriptase in milk, which sediment together as particles that are similar in density to

Fig. 4. Nucleic acid hybridization demonstrating tumor virus RNA and DNA in human breast tissue.
Virus Natural Host Tumor Association Type of Tumor Evidence for Oncogenic Potential

| Virus                  | Natural Host | Tumor Association | Type of Tumor | Virus Isolation from Tumor Cells | Tumor Induction by Isolated Virus | Seroepidemiological Evidence | In Vitro Transformation of Cells | Oncogenes of Transformed Cells |
|------------------------|--------------|------------------|---------------|----------------------------------|----------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Marek’s Disease        | Fowl         | Marek’s Disease  | Lymphoma      | +                                 | +                                | +                             | 0                             | 0                             |
| Lucke’ Frog Virus      | Leopard Frog | Lucke’ Frog      | Carcinoma     | +                                 | +                                | nd                            | 0                             | 0                             |
| Epstein-Barr Virus     | Man          | Burkitt’s Lymphoma | Lymphoma     | +                                 | +                                | +                             | +                             | + Mor                         |
| Herpes Simplex Type 2  | Man          | Cervical         | Carcinoma     | +                                 | 0                                | +                             | +                             | +                             |
| Herpesviruses Saimiri  | Squirrel     | Monkey           | Lymphoma      | +                                 | +                                | +                             | 0                             | 0                             |
| Herpesviruses Ateles   | Spider       | Monkey           | Lymphoma      | +                                 | +                                | +                             | 0                             | 0                             |

+ = positive results  
0 = negative results  
= rare, unconfirmed report  
nd = no data

Table 1. Herpesviruses with Known or Suspected Oncogenic Potential

mouse mammary tumor virus.\(^5\)

Human breast cancer tissue has also been intensively examined for virus components. In contrast to malignant mouse cells, human cells do not release infectious virus; however, there is evidence for at least some virus functions in human breast cancer tissue. Molecular hybridization techniques have shown common sequences between human cancer RNA and the DNA of mouse mammary tumor virus, but not of C-type oncornaviruses. (Fig. 4.) In addition, sera from many women with breast cancer have been shown to contain antigens serologically related to mouse mammary tumor virus.

Although these findings are not universally accepted as proof of a human oncornavirus analogous to the mouse mammary tumor virus, it is probable that such a virus exists and is fairly ubiquitous. Whether or not this virus is etiologically associated with human breast cancer, however, remains speculative. Putative virus functions in human milk have no apparent correlation with a family history of breast cancer despite the observed familial clustering of the disease, arguing against a viral etiology. Furthermore, epidemiologic surveys indicate that genetic factors acting via hormone (particularly estrogen) regulation are important in governing the incidence of breast cancer, and that breast feeding of infants is unrelated to cancer development later in life. Such results are inconsistent with a horizontally transmitted "milk factor" analogous to...
the mouse mammary tumor virus.

Thus, despite over half a century of research, scientists are as yet unable to find convincing evidence of an oncornavirus etiology for a single tumor in man.

**HERPESVIRUSES**

**Characteristics**

Several herpesviruses, previously thought to be non-oncogenic, have recently shown malignant potential in animals and man. (Table 1.) Human herpesviruses have been studied for a considerable time and, since they grow well in cell culture, the search for an association with cancer is considerably easier than that for a human oncornavirus.

The structure of all herpesviruses is probably similar, consisting of a DNA core with a molecular weight of approximately $10^8$ daltons within a multilayered capsid of 162 icosahedrally arranged subunits. The nucleocapsid is enveloped by one or more "membranes" containing glycoproteins and lipids. Glycoproteins resembling those of the virion are inserted into the plasma membrane shortly following infection.

Primary herpesvirus infections, which may be sub-clinical or acute, are often followed by recurrences that do not appear to be the result of repeated exogenous re-infection. On the contrary, the virus seemingly persists within the host after primary infection, although in what form remains controversial. Peripheral blood leukocytes and central nervous system cells seem to be favorite sites of virus persistence. Latent herpes might exist as whole virus particles, sub-viral units, or virus DNA which may or may not be integrated within the host chromosomes. It is unclear how the virus survives and gives rise to recurrent disease in the
presence of high titers of neutralizing antibody, and a supposedly good immune system. Although the mechanism involved is obscure, latent herpes presumably persists within the cell without causing cytopathic effects. This fact is important considering the recent evidence implicating several herpesviruses in oncogenesis; since cell death is inevitable following productive herpesvirus infection, malignant transformation can only occur in a non-productively infected cell capable of division and growth. Cells of the central nervous system do not divide and, given the predilection of herpesviruses for peripheral blood leukocytes, it is perhaps no coincidence that lymphomas have been associated with herpesviruses.

**Role in Animal Tumors**

One of the first herpesviruses to be linked with cancer causes Marek's disease, a highly infectious, malignant lymphoproliferation in fowl. Virus from tumor cells passaged in chicken
kidney or duck embryo cells in culture will subsequently induce tumors in new hosts. The virus does not complete its life cycle in tumor cells; rather, infected feather follicle cells produce virus which is shed in dust and dander, and transmitted to susceptible birds via the upper respiratory tract. However, relatively few infected birds develop lymphoma. The importance of the host’s immune system in controlling Marek’s disease has been amply demonstrated by the efficacy of prophylactic immunization with an attenuated virus vaccine in eradicating the disease. Immunized birds still grow virulent virus to a limited extent, but tumor development is prevented. Of course, successful immunization against Marek’s disease in fowl raises the possibility of prophylactic immunization against herpesviruses in man.

Evidence suggests a herpesvirus etiology of renal adenocarcinoma in Lucké frogs, lymphoma in cottontail rabbits and possibly cattle and guinea-pig lymphomas. However, in addition to Marek’s disease, the best support for an association between herpesvirus and cancer is provided by the study of two primate lymphomas. Herpesvirus saimiri has been isolated from healthy squirrel monkeys, and herpesvirus atelis from healthy spider monkeys. These viruses, which do not cause cancer in the natural hosts, induce malignant lymphomas when inoculated into other monkey species, particularly marmoset monkeys. Induced tumor cells release infectious virus when cultured in vitro; this virus then produces tumors in other susceptible animals. As in Marek’s disease, the host’s immune response to the virus apparently plays a crucial role in determining whether a tumor develops. Tumor resistance seen in some species, including the natural host of the virus, is attributed
to rapid production of neutralizing antibody, in contrast to the much slower immune response in tumor susceptible monkeys.

**Epstein-Barr Virus and Burkitt's Lymphoma**

Animal systems associating herpesviruses with the development of malignant lymphoma provide an informative background to understanding the Epstein-Barr herpesvirus (EBV) and its relationship to human lymphoma, particularly Burkitt's lymphoma. More than 10 years ago, epidemiologic investigations implicated an infectious agent, possibly with an insect vector, in the etiology of this malignant tumor of the jaw, prevalent among children in West Africa. The Epstein-Barr herpesvirus, discovered in cultured tumor cells, is able to "transform" normal human leukocytes in vitro. These transformed cells, which have a lymphoblastoid appearance similar to Burkitt's tumor cells, are capable of unlimited growth in culture, unlike normal leukocytes which senesce and die after a few cell generations.7

Direct evidence of EBV in Burkitt's lymphoma is lacking, but during the last few years significant circumstantial clues have been accumulated. Biopsy specimens from most Burkitt's lymphomas contain Epstein-Barr virus DNA, detected by nucleic acid hybridization to a radioactive virus RNA or DNA "probe." Cells from other tumors rarely show evidence of EBV DNA, except for nasopharyngeal carcinoma and Hodgkin's disease, which are also associated with this herpesvirus. Burkitt's tumor cells also show EBV-associated antigens. One, the "membrane antigen" (MA), is found on the membrane of tumor cells, but not on bone marrow cells from the same patient. A second "EB nuclear antigen" (EBNA), is found in the nucleus of most Burkitt's cells. (Fig. 5, p. 222.) Virus capsid antigens (VCA) and virus particles are undetectable in tumor biopsy material, but frequently appear in tumor cell lines, albeit in a small percentage of the cells in any line. Despite the low frequency of mature virus production, cloning experiments have shown that all cells in every tumor line contain the EBV genome and the potential to produce virus antigens or complete virus.

Individuals who have been exposed to EBV have serum antibodies to several different viral antigens. Serological studies of patients with Burkitt's lymphoma and infectious mononucleosis—now also associated with the Epstein-Barr virus—demonstrated that changes in antibody titer to these various antigens can be correlated to diagnosis, prognosis and changing clinical status.8 (Table 2.) After primary infection with EBV, healthy individuals maintain low titers of antibody to VCA, MA and EBNA; antibody to early antigen is rarely observed. However, antibody to the restricted "R" component of early antigen and very high titers of anti-VCA are found in patients with Burkitt's lymphoma. Furthermore, long-term studies of these patients in remission have shown that high titers of anti-MA and low titers of anti-EA correlate with good prognosis. The converse correlates with a high chance of tumor recurrence and, in fact, decreasing titer of anti-MA has repeatedly preceded fatal relapse.

These rather complicated serological tests imply that the EB virus plays an active role in Burkitt's lymphoma, and that it is not merely a passenger virus. EBV's oncogenic potential has recently been confirmed by the production of malignant lymphomas, resembling reticulum cell sarcomas, in marmoset and owl monkeys after inoculation with the virus or EBV-containing lymphoid cells.

If the Epstein-Barr virus is oncogenic and induces Burkitt's lymphoma, two important questions remain to be an-
Antigen | Presence in Burkitt’s Lymphoma Cells | Presence in Cultured Burkitt Cells
--- | --- | ---
Virus Particles | No | Some lines, small percent of cells
Virus Capsid (VCA) | No | Some lines, small percent of cells
Membrane Antigen (MA) | Yes | Yes, most cells
Early Antigens (EA) | No | Yes
R and D Component | Yes | Yes
EB Nuclear Antigen (EBNA) | Yes | Yes

AntigenPresence in Burkitt’s lymphoma cells has been explained by postulating cell fusion between lymphocytes and epithelial cells of the upper respiratory tract, possibly mediated by myxoviruses. An analogous situation is the in vitro experimental fusion of EBV-carrying lymphoid cells and epithelial cells by inactivated Sendai virus (a myxovirus). The hybrid cells retained an epithelial morphology, but carried EBV genes which were expressed under certain experimental conditions.

**EBV and Nasopharyngeal Carcinoma**

Another tumor associated with the Epstein-Barr virus is nasopharyngeal carcinoma, a rare epithelial tumor prevalent in Chinese. Since this tumor occurs most often in adults and, since most adults are seropositive for EBV antibodies, seroepidemiological surveys are almost impossible. However, the consistent presence of EBV DNA in nasopharyngeal carcinoma cells, and the abnormally high titers of anti-EBV antibody in tumor patients suggest a virus-tumor association. The presence of the strongly lymphotropic EB virus in epithelial carcinoma cells has been explained by postulating cell fusion between lymphocytes and epithelial cells of the upper respiratory tract, possibly mediated by myxoviruses. An analogous situation is the in vitro experimental fusion of EBV-carrying lymphoid cells and epithelial cells by inactivated Sendai virus (a myxovirus). The hybrid cells retained an epithelial morphology, but carried EBV genes which were expressed under certain experimental conditions.

**Herpes Simplex Type 2 and Cervical Carcinoma**

Perhaps the most common and most extensively studied of the human herpesviruses is herpes simplex. Two subtypes have been distinguished based on immunological specificity, growth characteristics in culture, base composition of DNA, and site of infection in the human body. Type 1 virus has been isolated mainly from oral lesions; type 2 virus, from genital lesions.

Direct evidence that herpes simplex virus type 2 (HSV-2) causes cervical cancer is almost impossible to obtain. However, seroepidemiologic studies
have repeatedly shown that type 2 infections and cervical carcinoma frequently occur in similar groups of women, both diseases behaving as though venereally transmitted. In general, antibodies to HSV-2 are found more often in women with cervical cancer than in healthy women or women with non-malignant gynecological disorders—age, race and socio-economic status being constant. Antibody to other venereal disease agents does not correlate with cervical cancer. An association between anti-herpes simplex virus type 2 antibody and pre-invasive cervical lesions has also been noted, although it varies considerably by study and stage of disease. Some of this diversity is undoubtedly due to real differences in populations, but much of it must also be attributed to variations in serologic methods. Nevertheless, statistical analysis confirms that the association between HSV-2 and cancer of the cervix does not represent a covariant of sexual promiscuity, other venereal diseases, race or socio-economic status.

A number of as yet unconfirmed reports suggest that HSV-2 genetic information may be present in cervical carcinoma cells. Herpes simplex virus type 2 DNA has been detected by nucleic acid hybridization and herpes-specific antigens have been described. In addition, infectious herpes simplex has been recovered from a line of cultured carcinoma in situ cells. Cervical abnormalities have also been found in mice and monkeys inoculated genitally with HSV-2.

The oncogenic potential of herpes simplex viruses types 1 and 2 has recently been further demonstrated by the in vitro transformation of normal cells and the subsequent induction of tumors in susceptible hosts. Since herpes simplex virus is cytopathic, its transforming potential cannot normally be expressed in infected cells. However, ultraviolet irradiation or photodynamic inactivation can damage the viral nucleic acid and prevent the production of infectious progeny. Cultures of primary hamster embryo fibroblasts exposed to inactivated virus show no cytopathic effects. Yet, after two to four weeks, foci of “transformed” cells appear against a background of normal cells. These foci can be isolated and grown in continuous culture. Using this technique, four of 21 isolates of
HSV-1, and 11 of 22 HSV-2 isolates have shown transforming ability. (Fig. 6, p. 223.)

The transformed lines, of epitheliod or fibroblastoid morphology, contain cells that have detectable herpes-specific antigens and virus-directed RNA. Newborn hamsters inoculated with several of the transformed lines developed tumors containing herpes-specific antigens and, moreover, neutralizing antibody to the virus. Cells transformed by both HSV-1 and HSV-2 have induced tumors in hamsters. It may be particularly significant that a HSV-1 transformed epitheliod line induced rapidly metastasizing adenocarcinomas which more closely resemble common solid tumors than do the sarcomas induced in most experimental systems. (Fig. 7, p. 224.)

Several laboratories have confirmed the transforming ability of herpes simplex in mouse and human cells under conditions that restrict virus growth. Apart from their possible significance to clinicians who treat herpetic lesions by ultraviolet irradiation or photodynamic inactivation, these results clearly demonstrate that herpes simplex is a potential human cancer virus.

Nevertheless, the evidence is, at best, suggestive and considerable study is still necessary. In particular, prospective screening programs would be useful to determine the actual risk of cervical cancer in women exposed to HSV-2, and to evaluate changing antibody patterns to virion and non-virion antigens in determining the diagnosis and prognosis of cancer.

Conclusions

There is a good deal of circumstantial evidence linking RNA- and DNA-containing viruses with human cancer. Yet, despite the expenditure of many man-hours and millions of dollars, not a single human cancer has a proven viral etiology. Why has so little success been achieved? Why is it difficult to find a human oncornavirus? If most candidate human tumor viruses are ubiquitous, why do the majority of people not get cancer?

Because it is impossible to induce tumors in man, the study of human neoplasia has been somewhat hampered. Indeed, the first priority of a clinician is to destroy the tumor as quickly and completely as possible. Prior to the development of colonies of inbred mice and the use of newborn animals for experimental inoculation, virologists were also unable to find oncogenic viruses in mammals. However, “wild” oncornaviruses have recently been isolated from outbred animals such as the cat and it is highly probable that, despite the difficulties involved, human oncornaviruses will soon be identified. But whether any such virus will ever be directly proven oncogenic in man is doubtful. Perhaps the best proof of a viral etiology of cancer would come from the development of anti-virus vaccines. The example of Marek’s disease suggests that, for herpesviruses at least, the possibility of vaccine development is not remote, although preliminary studies have not been encouraging. Once again, ethical restraints on the use of intact killed or attenuated virus vaccines should be considered.

It is probable that viruses involved in cancer are frequently defective, and virus genetic material within the malignant cell may consist of only a few “transforming” genes, representing a fragment of the whole genome. This might explain why it has often been difficult to detect complete virus or virus products in both RNA and DNA transformed or tumor cells. To circumvent this problem, many laboratories are now using more sensitive techniques for detecting small amounts of viral RNA and DNA within cells, and for examining the transforming potential of viral nucleic acid fragments.

Although exposure to most candidate
human tumor viruses appears widespread, many people never develop cancer, and many more do not have the disease until late in life. In fact, evidence of human oncornavirus information has been found in normal breast tissue, and infection with EBV and herpes simplex occurs in most individuals tested. If these viruses do play a role, other factors must be operating to control oncogenic expression. Genetic predisposition to cancer has been clearly shown in mice and chickens for both leukemia and Marek's disease. Examples of genetic factors in human cancer include the high incidence of nasopharyngeal carcinoma among Chinese in different environments, and the susceptibility of patients who are found to have certain chromosome abnormalities to leukemia.

Whether or not cancer develops following viral infection probably depends on the immunologic response of the infected animal. Such is the case in Marek's disease, Burkitt's lymphoma and monkey lymphomas. The importance of the immune response is also seen by the increased incidence of cancer in people who, whether due to age, disease or immunosuppressive therapy, have reduced immunocompetence. In addition, environmental hazards, such as irradiation and exposure to carcinogens, may activate the oncogenic potential of latent viruses.

Finally, the common disease manifestation of many viruses is only one of numerous consequences of infection. Herpesviruses are particularly "multipotential." For example, herpes simplex type 1 may cause fever blisters, encephalitis, keratoconjunctivitis, or no symptoms at all. As a result of "stress," the latent virus in the trigeminal ganglia of the host can recur causing a similar variety of symptoms. During long periods of latency, the dormant virus might change into a form with increased potential. Indeed, it would not be surprising if "stress" sometimes involved host or environmental conditions which favored malignancy. Thus, cancer may be an "accident," involving the convergence of multiple factors, viruses being of prime importance.

This is, however, speculation. The only conclusions which can be drawn from extensive data are that a number of human viruses have oncogenic potential, and that more will be discovered in the near future with the identification of human oncornaviruses. In several human tumors, an oncogenic virus appears to be a necessary, but not a sufficient, condition for tumor development. The expression of the oncogenic potential of the virus is controlled by a number of factors, most of which, like all pathogenesis, are not completely understood.

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