Viruses and Human Cancer

JOHN P. MANOS, M.D. and ERNEST M. WALKER, JR., M.D., PH.D.

Department of Laboratory Medicine, Medical University of South Carolina, Charleston, SC 29425

ABSTRACT

The cause of human cancer is probably multifactorial and the role of viruses is unclear. The study of retroviruses has led to the identification of oncogenes responsible for transformation and tumor induction. Human viruses associated with malignancies include the JC virus (associated with progressive multifocal leukoencephalopathy) and some adenoviruses. No human malignancies have been associated with the latter group. A number of herpes viruses of lower animals have been associated with malignancies and herpes simplex virus type 2 has been associated with carcinoma of the cervix and vulva. The Epstein-Barr virus has been associated with Burkitt's lymphoma and nasopharyngeal carcinoma. Some circumstantial evidence suggests that cytomegalovirus may be associated with Kaposi's sarcoma among homosexuals. The hepatitis B virus (HBV) has been associated with hepatocellular carcinoma. The fulfillment of Koch's postulates presents ethical problems regarding man and proving the viral etiology of human malignancy. Social experiments may elucidate some of these questions. An increase in venereal herpes should be associated with an increase in carcinoma of the cervix and use of the HBV vaccine in populations with high incidences of HBV carrier states should decrease the incidence of hepatocellular carcinoma. The investigation of the retroviruses though not establishing viruses as causing human malignancies at least will improve our understanding of the malignant process.

That a particular human cancer is caused by a virus is yet to be proven. The cause of human cancer is probably multifactorial in that environmental, physical, and chemical stimuli, with perhaps specific genetic factors in the right combination, can bring about malignant changes. If and how viruses or viral products play a role in the development of human malignancy is under intense investigation. It is well established that a number of viruses of lower animals are able to cause malignancies in the natural host or in other species. It would be ludicrous to expect that viruses do not play a role in the development of human cancer.

The causal relationship between viruses and human cancer is difficult to establish and the fulfillment of Koch's postulates to prove the infectious etiology of some cancers remains difficult if not impossible. Intensive investigation attempting to demonstrate the causal re-
relationship between viruses and human cancer provides only circumstantial evidence. The identification of virus particles, virus precursors, or virus specific nucleic acid from biopsies or cultured tumor cells of human origin does not prove that a virus has caused the malignancy. A significant problem with this approach is that the virus may merely be a passenger or a contaminating virus. The attempt to induce tumors in animals by the inoculation of human tumors or extracts of human tumors, in an effort to demonstrate a candidate human virus, is limited. Animal viruses natural to the host injected may have been introduced. Human viruses are able to cause malignant transformation in vitro and are potential suspects as human oncogenic viruses. Significant inferences have been acquired from seroepidemiological surveys in an attempt to correlate viral antibody with tumor incidence, examples being the Epstein-Barr virus (EBV) and its association with Burkitt's lymphoma and herpes simplex virus type 2 (HSV-2) and carcinoma of the cervix.

A number of animal and human viruses have been associated either directly or indirectly with oncogenesis and malignancies. The retroviruses (oncornaviruses) are a large heterogenous group of small ribonucleic acid (RNA) containing viruses that infect many animal species (possibly including man) and in many instances are proven to be oncogenic in their natural host or in other animal species. Among the human viruses which have oncogenic potential at least in other animal species are the papovaviruses, the adenoviruses, and some herpesviruses. An important characteristic of many tumor causing viruses is the ability to cause transformation (i.e., the transforming of a normal cell into a malignant state). Characteristics of transformed cells include the capability to grow indefinitely in culture, the loss of contact inhibition, the alteration of the host cell membranes and, frequently, the capacity to induce tumors in laboratory animals.

One of the most studied group of viruses with oncogenic potential among many of its members are the retroviruses. These viruses contain single stranded RNA and range from 80 to 110 nanometers in size. They contain deoxyribonucleic acid (DNA) polymerase (a reverse transcriptase) which causes the formation of double stranded DNA which is produced from a RNA template. This is a reversal of the usual direction of genetic information which is DNA to RNA. This DNA intermediate is then integrated into the host genome which subsequently may lead to neoplastic transformation. This new characteristic is perpetuated to the progeny of the transformed cell. The mechanism by which this occurs is poorly understood. One of the well known viruses in this group, the Rous sarcoma virus (RSV) has been studied extensively. The RSV virus is known to contain four genes, one of which has been termed the src (for sarcoma) gene or oncogene which carries the information needed for transformation. Evidence suggests that the src gene produces a kinase which is important in the phosphorylation of tyrosine which is involved in cell glycolysis. Since transformed cells make 50 times as much viral kinase as normal cells there is an increase in glycolysis in the transformed cell. There are some 15 oncogenes which have been described among the various retroviruses. Similar evidence of an src like gene has been found in vertebrate cells, including cells from a human bladder carcinoma. In vertebrates these cellular type src genes are called c-src or 'cell oncogenes' as opposed to v-src for 'viral oncogenes'. The c-src genes are similar in size and in chemical structure to their viral counterparts. Both catalyze phosphorylation of tyrosine and both apparently are tightly bound to the plasma membrane of cells.

One hypothesis as noted previously is
that the c-src gene is a normal and necessary part of the cell and is involved in the normal growth and development of the cell. However, under proper stimulation, that is by a carcinogen, be it chemical, radiation, or possibly even a non-oncogenic virus, the activity of the c-src gene is augmented and results in an inappropriate expression resulting in uncontrolled or cancerous growth. This theory is referred to as the dosage hypothesis. An alternative hypothesis is that viral oncogenes differ from their cellular progenitors in subtle but important ways as a result of mutations when cellular genes were copied into the retrovirus genomes possibly through viral infection early in evolution. Thus, the v-src and c-src oncogenes might have different targets in the cell and, therefore, different effects on cellular behavior. The finding of oncogenes similar to those in retroviruses in human cells, however, is difficult because of the enormous size of the DNA in the human genome. Recent reports have shown serological evidence of antibody to a human retrovirus associated with human T-cell lymphoma leukemia virus (HTLV) in a cluster of Japanese with adult T-cell leukemia. Antibody was not found in those with non-T-cell leukemia, in healthy donors in the endemic area and in random donors.

Do oncogenic viruses have to have oncogenes? Apparently not, since some known tumor viruses lack an oncogene. They do have somewhat different characteristics than those tumor viruses possessing oncogenes in that the former act slowly in animals, taking several months for a tumor to develop, and do not have the characteristic of causing transformation of normal cells in vitro. Do human viruses, which have at least circumstantially been associated with human cancer, have oncogenes such as EBV and HSV-2? Both are transforming viruses; therefore, oncogenes should be part of the genome. Many investigators are trying to identify such genes in these viruses. The case with human viruses and proven causation of cancer in man continues to be elusive; however, a number of human viruses have been associated indirectly with malignancies although, as of this writing, there is no definitive evidence that any virus is, in fact, the causation of cancer in man.

The papova group of viruses have a number of member viruses that can cause transformation and induce tumors in laboratory animals. Included in this group of viruses is the human papilloma virus (wart virus) which is a tumor virus; however, it is not associated with malignancies. The JC virus is associated with progressive multifocal leukoencephalopathy (PML) and occurs in patients with immunosuppressive disease secondary to malignancies such as Hodgkin's disease. This virus, which has been isolated from a number of patients, induces brain tumors in newborn hamsters, histologically resembling malignant glioblastomas. It apparently is an ubiquitous virus among humans since antibody to this virus is present in up to two-thirds of children by the age of 14 years. Condyloma acuminata (venereal warts), caused by an antigenic variant of the human papilloma virus, has been demonstrated to undergo malignant transformation.

Other viruses in the papova group such as the polyoma and the SV40 viruses have been shown to produce cancers in a variety of laboratory animals. A number of human adenoviruses are also known to cause a variety of malignancies in newborn rodents, the most oncogenic being types 12, 18 and 31. However, there is no evidence that adenoviruses are oncogenic in man.

There are several herpes viruses of lower animals that have been definitively associated with malignancies. Marek's disease is an infectious malignant lymphoproliferation in fowl and has recently been controlled by an attenuated viral vaccine. The Lucké frog virus is known to be the etiological agent of renal ad-
enocarcinoma in frogs. Herpes viruses of lower primates are also associated with carcinoma, including herpesvirus saimiri which has been isolated from healthy squirrel monkeys and herpesvirus ateles isolated from healthy spider monkeys. Neither of these viruses causes cancer in their respective natural hosts but both induce malignant lymphomas in other monkey species. Apparently the host immune response plays a crucial role in preventing the host from developing the malignancy. A common sexually transmitted disease among humans, HSV-2, has been, in the past several years, associated with carcinoma of the cervix; however, most of the incriminating evidence has been seroepidemiological. Genital HSV and cervical carcinoma frequently have been found to occur in similar groups, and antibody to HSV-2 has been found more often in females with cervical carcinoma than in healthy females. Antibodies to other venereal diseases do not correlate with cervical carcinoma as do HSV-2 antibodies. The oncogenic potential of HSV-2 has also been demonstrated by the fact that it can cause transformation of normal animal and human cells in vitro and these cells in turn have induced tumors in new born laboratory animals. There have also been recent reports demonstrating HSV-2 type antigens in association with squamous cell carcinoma in situ of the vulva (9 of 10 patients in one reported series). The rise in squamous cell carcinoma of the vulva and genital HSV-2 suggests an association. On the other hand, this also may merely be a reflection of an opportunistic infection by an ubiquitous agent among man.

The EBV is one of the most common viruses that affects man. This virus selectively infects the B lymphocytes of man and, like HSV-2, causes in vitro transformation. Transformed cells by the EBV show oncogenicity when inoculated into monkeys. There is also significant seroepidemiological evidence associating the EBV with malignancies, including Burkitt’s lymphoma in Africa and nasopharyngeal carcinoma in the oriental male and with infectious mononucleosis in the United States. Recently, there has been an association of the EBV with other malignancies, such as lymphomas following renal transplantation and with acute leukemias associated with infectious mononucleosis. It is interesting that of the herpesviruses mentioned only the EBV and HSV-2 have the ability to transform normal cells in vitro. All of the viruses in the Herpes group are able to induce tumors by the isolated virus, except for HSV-2, with results for the latter virus being equivocal.

Another member of the Herpes group of viruses, the cytomegalovirus (CMV) has received much attention in the recent literature regarding its association with Kaposi’s sarcoma occurring in an almost epidemic form among the homosexual population. This sarcoma tends to occur in those individuals who have what has recently been termed an ‘acquired immunodepressive syndrome’ (AIDS). Although other chronic infections also occur in the homosexual population, especially Pneumocystis carinii induced pneumonitis, CMV apparently is one of the common threads that has seroepidemiologically been associated with patients having Kaposi’s sarcoma. Infection with CMV has been shown to cause immunosuppression and its genome has been detected in Kaposi’s sarcoma tissue. The virus, after ultra violet irradiation, can cause transformation of normal hamster fibroblasts into tumor cells.

Finally, the Hepatitis B virus (HBV) has been associated with hepatocellular carcinoma (HCC). In a recent study investigating 20 patients who died with alcoholic cirrhosis and HCC, all had HBV DNA integrated into the genome of the neoplastic liver cells, as demonstrated by hybridization studies, although only 9 of
16 of these patients whose blood was available were found to contain serological markers of HBV infection. The occurrence of HCC tends to correlate somewhat with the incidence of chronic carriers of HBV. In areas such as the United States where the incidence of the carrier state is low so is the incidence of HCC. Ongoing epidemiological studies of oriental male HBV carriers over the past two to four years have shown that 50 cases of HCC have occurred during this period, and all but one occurred in chronic carriers. The investigators, from following this group to date, estimate that the relative risk of HCC is more than 250 times greater in carriers than in non-carriers. Again, HBV may only be one of many hepatotoxic agents that may eventually lead to HCC and that HBV is, in fact, a cause of HCC remains to be proven.

There is at present no conclusive evidence that viruses cause human tumors. However, with the knowledge gained from the study of oncogenic viruses of lower animals and with a number of Herpes viruses in man being strong suspect, it seems inconceivable that at least some human malignancies are not caused directly or indirectly by viruses. It is probable, as many feel, that the cause of human malignancy is multifactorial and that a variety of circumstances, such as genetic predisposition, the state of the immune system, environmental exposure and the presence of certain viruses, all must occur at the right time and the right place in order for a malignancy to develop. The fulfillment of Koch's postulates presents ethical problems regarding man and definitive proof of the viral etiology for human cancer must come by other indirect or possibly natural mechanisms. The use of an attenuated virus vaccine in successfully eradicating Marek's disease in fowl is well documented. Analogous vaccines for humans is, of course, complicated by the safety factor. The administration of the newly developed HBV vaccine to populations with high incidences of HBV carrier states should, in time, demonstrate a decrease in the incidence of HCC in these populations if HBV is a major factor in the development of this malignancy. Since there appears to be an increase in venereal transmitted HSV-2 world wide and since it has been incriminated as a possible causation of cervical carcinoma, there should be an increase in cervical carcinoma in the next decade or two if this malignancy is associated with HSV-2.

The intense investigation of the tumor producing retroviruses has revealed much in the understanding of the malignant cell in lower animals and in man. Continued investigation in this area, although not revealing a definitive causation between viruses and human malignancies, will at least continue to give us a better understanding of the malignant process itself.

References
8. Henle, W., Henle, H., and Lennette, E. T.:


