Virus-Associated Cancers Can Be a Major Problem in the Tropics

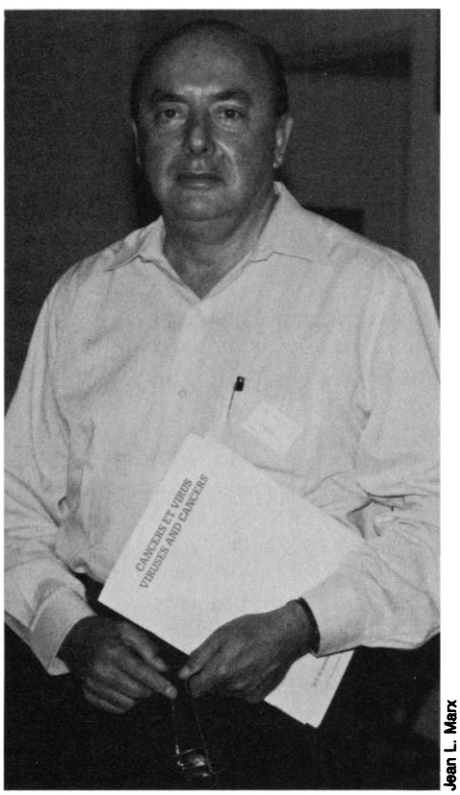
A recent meeting on "Viruses and Cancers,"* which was held on 8 to 10 January on the island of Martinique pointed up the growing consensus that viruses contribute in a major way to the development of several human cancers, especially in the tropical regions of the world. According to meeting co-organizer Jacques Crozemarie of the Centre Technique pour le Soutien de la Recherche sur le Cancer in Villejuif, as many as one cancer out of every two in some parts of the world may be virus-associated.

The cancers in question include liver carcinoma, which has been associated with hepatitis B virus; cervical cancer, which has been linked to certain strains of human papilloma virus; adult T-cell leukemia, which is caused by human T-cell lymphotropic virus I (HTLV-I);† and Burkitt's lymphoma and nasopharyngeal carcinoma, both of which have been associated with the Epstein-Barr virus.

Data compiled by the World Health Organization (WHO) give an indication of the magnitude of the possible contribution of viruses to the cancer problem. Cervical cancer, with 450,000 to 500,000 cases every year throughout the world, is the fifth most common cancer, and, says Nicholas Day of WHO's International Agency for Research on Cancer in Lyon, "It is the most common cancer in women in most of the developing world." The 250,000 cases of liver cancer make it eighth on the worldwide cancer list, although its incidence is especially high in some areas, including southern China.

Yi Zeng of the China National Center for Preventive Medicine told the meeting participants that there are more than 100,000 annual cases of liver cancer in China, most of them in the southern part of the country. In addition, there are nearly 53,000 cases of cervical cancer and about 19,000 cases of nasopharyngeal cancer. All in all, nearly one-third of China's 700,000 annual cases of cancer are virus-associated, with that percentage reaching 50 to 60 percent in southern China. In contrast, according to figures compiled by the American Cancer Society, some 45 percent of the cancers in the United States are carcinomas of the lung, colon-rectum, and breast, which are not thought to be virus-linked.

With the possible exception of HTLV-I, little is known about how the viruses that have been associated with the human cancers might cause cells to become malignant. The DNA's of all the viruses have been found consistently in the tumor cells. In this way, they resemble the viruses that cause cancers in laboratory animals. However, many of the animal cancer viruses act very quickly, presumably because they carry oncogenes that can make cells malignant in a single step, whereas the human cancer viruses work much more slowly and the associated cancers usually do not appear until many years after infection. Nevertheless, there are indications that at least human papilloma virus carries a potential oncogene (see briefing, p. 920).



Jean L. Marx

Jacques Crozemarie

Co-organizer of the "Viruses and Cancers" meeting.

Participants in the Martinique meeting unanimously stressed that the human cancer viruses do not cause the cancers by themselves. Other factors, such as environmental carcinogens, cigarette smoke, diet, heredity, additional infections, and the status of the individual's immune system, also contribute.

Nevertheless, if infection by a virus is even one of several factors that contributes to cancer development, then the way is open to preventing the cancer by preventing the infection.

*The meeting was cosponsored by the French Association pour la Recherche sur le Cancer, the National Institutes of Health, and the National Cancer Institute.
†A previous report (*Science*, 31 January, p. 450) covered the portion of the Martinique meeting dealing with the HTLV's.

Progress on a Vaccine for Epstein-Barr Virus

The apparent contribution of certain viruses to cancer development has given new impetus to efforts to produce vaccines that will prevent the viral infections. At the meeting, M. A. Epstein described the progress of his group at the University of Bristol School of Medicine toward developing a vaccine for the Epstein-Barr virus (EBV), which has been linked to two human cancers. One of them, Burkitt's lymphoma, is relatively rare. Most of the 5,000 to 10,000 annual cases occur in the malarial regions of Africa. Nevertheless, in those regions it is the most common childhood malignancy, Epstein points out. The other cancer, nasopharyngeal carcinoma, is much more widely distributed. There are at least 50,000 cases worldwide every year, according to WHO estimates, and these occur mainly in Southeast Asia, southern China, northern Africa, and among the Eskimos.

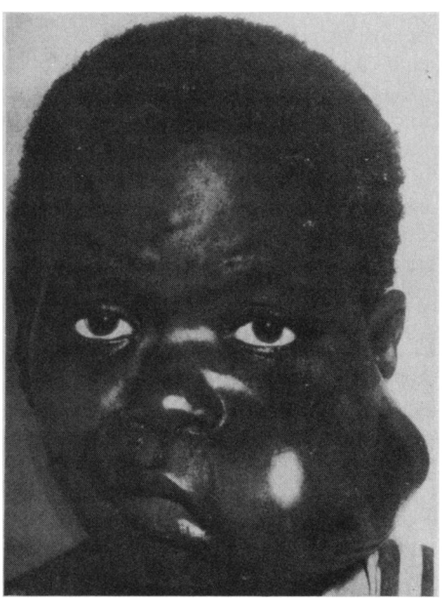
Because of the possibility that EBV DNA may be carcinogenic even if the virus is killed or attenuated, making a vaccine from the complete viral particle would be unwise. Epstein and his colleagues have chosen to use instead a large glycoprotein from the outer membrane of the virus. The glycoprotein has a molecular weight of 340,000 and is designated gp340. People who have been infected naturally by EBV make antibodies to gp340 that can neutralize the virus. Moreover, Marek's disease virus is, like EBV, a herpesvirus and causes a lymphoma in chickens. Other investigators have shown that vaccination with the gp340 equivalent from Marek's disease virus prevents the birds from getting the lymphoma.

Epstein and his colleagues have now tested two different gp340-bearing membrane preparations in cottontop tamarins, a species of New World monkey that ordinarily develops a malignant lymphoma within a few weeks after infection by EBV. One of the preparations consisted simply of membranes taken from infected cells, which would not be suitable for human use because they might be contaminated with whole viral particles. The other consisted of the artificial membranes called liposomes that had been impregnated with purified gp340. Both preparations elicited antibodies against

gp340 in the immunized animals, which were subsequently challenged with EBV doses sufficient to cause lymphomas in 100 percent of the control animals. The result showed, Epstein concludes, "that the vaccine is capable of protecting the animals against a massive dose of tumor-inducing virus."

For a human vaccine to be practical, there must be a reliable source of large quantities of pure gp340. The recent cloning of the gp340 gene by Michael Mackett's group at the Patterson Laboratory in Manchester, England, could provide a potential source of the protein by allowing it to be produced in bacterial or other cells.

Meanwhile, Mackett and his colleagues have inserted the gp340 gene into the vaccinia virus genome, thereby making a hybrid virus that might be used to immunize against EBV. Vaccinia virus has been safely



Burkitt's lymphoma patient

Tumors of the jaw are common in African patients with Burkitt's lymphoma.

administered for many years as a vaccine for smallpox. The Epstein group is beginning trials to determine whether the gp340-vaccinia hybrid can elicit protective immunity to EBV in animals.

Epstein says that it is difficult to predict when testing of an EBV vaccine in humans could begin, but estimates that it might be in as little as a year or two. The first step, he suggests, would be to determine in a few previously uninfected volunteers whether the test vaccine elicits the production of virus-neutralizing antibodies.

Although EBV infections in the developing countries occur in the first year or two of life, in the developed nations individuals usually do not get infected before adolescence or early adulthood. Under these conditions EBV does not appear to dispose to cancer but can cause infectious mononucleosis, which is temporarily debilitating but is not life-threatening. If the vaccine proves capable of eliciting neutralizing antibodies in the volunteers, then the next step might be to determine whether it prevents mononucleosis, Epstein says. If it also passes that test, then a clinical trial could be carried out in one of the African areas where Burkitt's lymphoma is a problem.

Human Papilloma Virus and Cervical Cancer

The human papilloma virus (HPV) group includes some 40 different members that cause a variety of abnormal growths. In general, says Gerard Orth of the Pasteur Institute in Paris, the individual HPV's are specific for the area of the body affected and the type of growth produced. Most cause benign conditions, such as the common warts that occur on the hands or the plantar warts that grow on the soles of the feet. Nevertheless, within the past few years an increasing body of evidence has linked certain of the HPV's with cervical and other cancers of the genital and anal areas.

The evidence that those HPV's contribute to the etiologies of the cancers includes demonstrations that the tumor cells contain viral DNA. "The majority, if not all, of cervical, penile, and vulval cancers carry HPV DNA," says Harold zur Hausen of the Deutsches Krebsforschungzentrum in Heidelberg, Germany. DNA from HPV16 is the most frequently found, occurring in about 50 to 60 percent of cervical cancers. Next most commonly found is DNA from HPV18, which is present in 15 to 20 percent of the cancers. The DNA's from HPV11, 31, 33, and 35 each occur in a few percent of the cancers.

Studies of cells that carry the HPV DNA are beginning to reveal how the viruses may contribute to cancer development. According to zur Hausen, integration of the viral DNA into the cellular genome may be one of the steps on the road to malignancy. He and his colleagues find that the DNA is not integrated in cervical cells that show early signs of abnormality but are not yet cancerous. It is integrated in cervical carcinoma cells, although some carry unintegrated copies as well.

Insertion of the HPV DNA into the cellular genome leads to the interruption of a region containing genes expressed early in the viral life cycle. As a result, several of the early genes cannot be expressed. There is also a possibility that expression of the remaining HPV genes may no longer be controlled normally. Peter Howley and his colleagues at the National Cancer Institute have shown that the E2 (for second early) gene from bovine papilloma virus participates in gene control and is inactivated when the bovine virus transforms cells to the cancerous state. The bovine E2 gene is in a region that may be analogous to that disrupted by integration of the HPV DNA.

Two of the early genes (E5 and E6) of bovine papilloma virus can transform cultured cells. Although the E5 gene of HPV is one of those knocked out by integration of the viral DNA, zur Hausen's group now has evidence that the E6 gene may also be a transforming gene. They have looked at a number of malignant cell lines that contain integrated HPV DNA and have found that the E6 gene is transcribed into messenger RNA in all of them.

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Moreover, they find that expression of the HPV early genes is apparently necessary for the malignancy of HeLa cells, which were originally derived from human cervical carcinoma cells and carry HPV DNA. If HeLa cells are fused with noncancerous cells, the hybrids continue to express the HPV early genes and maintain their malignant characteristics when grown in culture. However, if the hybrids are put into nude mice they are no longer malignant and, zur Hausen told the meeting participants, the early genes are no longer expressed.

Apparently the animals produce some factor that inhibits expression of the HPV genes. Cancers should only develop then when some additional change, either in the inhibitory factor itself or in the HPV-infected cells, results in a loss of the gene suppression. The suggestion that more than just viral infection is needed to convert cells to malignancy is consistent with the general view that development of human cancers is a multistep process.