relapse. If the antibody concentration did not decline, the prognosis for the patients was generally poor. Investigators think it unlikely that antibodies to a passenger virus (one that just happened to be present but was not causative) would be of prognostic value.

Although EBV particles are not found in Burkitt's lymphoma cells removed by biopsy, other traces of the virus can be detected. These include certain EBV-associated antigens and also viral DNA. Cellular DNA hybridizes either with viral DNA or with RNA transcribed from viral DNA. The results of the hybridization experiments indicated that each lymphoma cell contained multiple copies of EBV DNA. No one knows why the viral DNA is not completely expressed in tumor cells. It may be defective or partially repressed. A small number of cells in a few cultured cell lines derived from biopsied tumor cells did produce infectious viral particles or incomplete noninfectious particles. All of the cells, however, produced an EBV-associated nuclear antigen that may be analogous to the T (tumor) antigens produced in cells infected by oncogenic animal viruses such as SV40.

Another indication of the oncogenic potential of EBV is its capacity to transform lymphoid cells in culture. Normal lymphoid cells do not proliferate in culture and die out after a short time. Transformed cells, which harbor the viral genome, do grow in culture, and they have the characteristics usually associated with transformation, including loss of density-dependent inhibition of growth.

Production of cancer in laboratory animals with EBV would provide additional evidence that it causes related disease in humans, and would also provide a model system for studying therapeutic techniques. George Miller and his colleagues at Yale University induced lymphomas in a small number of marmosets by inoculating them with materials containing EBV. Although Miller has not conclusively proved that EBV itself caused the tumors, similarities between the human disease and that in marmosets make this the most likely explanation.

Herpesvirus saimiri, an oncogenic virus of nonhuman primates, may provide another model for investigating human lymphomas. This virus causes no overt disease in its natural host, the squirrel monkey, but induces lymphomas or occasionally lymphocytic leukemia in marmosets and owl monkeys. The behavior of the virus resembles that of EBV, both in its effects in living animals and in cultured cells. For example, neither EBV nor herpesvirus saimiri particles can be demonstrated in biopsied tumor cells but they are occasionally produced in cultured cells. Moreover, the antigen-antibody patterns associated with the latter virus resemble those of EBV.

Evidence implicating the herpes simplex viruses I and II (HSV I and HSV II) in the etiology of human cancer is similar to that outlined for EBV. Investigators have elucidated a series of correlations between certain types of cancer and past infections with the viruses, the presence of antibodies to virus-associated antigens, the presence of virus-associated antigens in tumor cells, and, in one case, the presence of viral DNA in tumor cells. The herpes simplex viruses also transform cells in culture.

These viruses are again familiar human pathogens. Herpes simplex virus I primarily infects regions around the lips (where it causes the common "cold sores"), the oral cavity, and the eyes. Herpes simplex virus II usually infects

What Is Cancer? What Forms Does

It is not yet clear whether cancer is many diseases exhibiting a common pattern of general symptoms or one disease that is manifested in many forms depending, primarily, upon the organ from which it evolves. In any case, more than 100 clinically distinct types of cancer are recognized, each having a unique set of specific symptoms and requiring a specific course of therapy. These types can, however, be grouped into four major categories:

► Leukemias are diseases in which abnormal numbers of leukocytes (white blood cells) are produced by the bone marrow. This enhanced production resembles the body's normal response to a massive infection, but in leukemias most of the leukocytes do not mature into functional cells. Leukemias are one of the most common malignancies of childhood, but they strike people of all ages. Preliminary results from the National Cancer Institute's Third National Cancer Survey of 1969 suggest that leukemias will account for about 3.4 percent of the 655,000 cases of cancer that will be diagnosed this year.

► Lymphomas are diseases in which abnormal numbers of lymphocytes (a type of leukocyte) are produced by the spleen and lymph nodes. The disease is thus quite similar to leukemia, but in some lymphomas the immature lymphocytes aggregate in the lymphoid tissues. Hodgkin's disease is the best-known form of lymphoma. The cancer survey indicates that lymphomas account for about 5.4 percent of diagnosed malignancies.

► Sarcomas are solid tumors growing from derivatives of embryonal mesoderm, such as connective tissues, cartilage, bone, muscle, and fat. Leukemias and lymphomas could be considered subgroups of sarcomas, since bone marrow and lymphoid tissues are derived from mesoderm. Sarcomas, leukemias, and lymphomas are the predominant forms of malignancy observed in laboratory animals and in cell cultures, but sarcomas themselves, according to the survey, account for only 1.9 percent of human malignancies.

► Carcinomas, solid tumors derived from epithelial tissues, are thus the major form of cancer. Epithelial tissues are the internal and external body surface coverings and their derivatives, and thus include skin, glands, nerves, breasts, and the linings of the respiratory, gastrointestinal, urinary, and genital systems. Carcinomas account for about 85.3 percent of malignancies. (The remaining 4.0 percent of malignancies include tumors derived from mixed tissues, such as ovaries and testes, and all others that are not readily classifiable.)

All of the more than 100 types share three major

genital areas and is transmitted venereally. Both may persist in the host for long periods of time and produce recurrent infections.

Beginning in the middle 1960's, epidemiological studies such as those conducted in the laboratories of André Nahmias at the Emory University School of Medicine, Atlanta, Georgia, Laure Aurelian at Johns Hopkins University School of Medicine, Baltimore, Maryland, and Joseph Melnick at Baylor College of Medicine, Houston, Texas, implied an association between HVS II, which Nahmias had identified as the cause of up to 95 percent of genital herpes infections, and cancer of the uterine cervix. Both conditions were correlated with increased numbers of sexual partners for the women surveyed. Women with cervical cancer had higher frequencies of antibodies to HSV II than did controls.

The problem with interpreting these results is that women likely to contract one venereal disease, genital herpes, might also be likely to acquire the other, cervical cancer. In other words, the two conditions could be independent consequences of a high degree of sexual activity. The solution to the problem requires close matching of women with cervical cancer and control women with regard to age, race, socioeconomic status, and all the variables indicative of sexual activity.

In one such study with carefully matched women, William Rawls, in Melnick's laboratory, found that women with antibodies to HSV II had a risk of acquiring cervical cancer more than twice as great as that of women without antibodies. There was no greater incidence of breast cancer in women with antibodies than in women without. Melnick concluded that the risk of developing cervical cancer appeared to be more closely related to HSV II infection than to attributes associated with number of sexual partners.

Virtually all epidemiological studies conducted to date have been retrospective ones in which the information about herpes infection was gathered after the onset of cancer. Nahmias and his associates are currently conducting a prospective study, begun in 1963, to determine whether women who have had genital herpes infection or who have antibodies to HSV II develop more cervical cancers than women who do not have the antibodies. The long latent period of cancer and the need to include large numbers of carefully matched women compound the difficulty of such studies. Nahmias' preliminary results indicate that women with antibodies to HSV II do have a higher incidence of cervical cancer than do women without antibodies. Women who were pregnant when genital herpes was diagnosed had an even higher incidence. Nahmias is now investigating whether changes in the female genital tract during pregnancy may predispose to initiation of cancer by HSV II.

Malignant transformation of cells by viruses probably depends on expression of some viral gene or genes. For adenoviruses and papovaviruses, substances called nonviron antigens are viral gene products thought to be associated with transformation. Nonvirion antigens are coded by the viral DNA but are not themselves part of the viral particles. Since they are foreign substances, the host species will make antibodies against nonvirion antigens that can be detected in blood serums.

Discovery of HSV nonvirion antigens in human tumor cells or of their antibodies in patients' blood serums would provide strong evidence for a causal role of these viruses in human cancer. Both antigens and antibodies have been detected. Albert Sabin, now

It Take? How Does It Kill?

characteristics that define cancer: hyperplasia, anaplasia, and metastasis. Hyperplasia is the uncontrolled proliferation of cells. Contrary to popular belief, however, hyperplasia does not imply an enhanced rate of proliferation: malignant cells display the same variations of rates as healthy cells. The malignant cells simply do not respond to the host organism's (as yet unknown) signals to halt division, and thus produce a localized accumulation of tissue.

Anaplasia is a structural abnormality in which the cells resemble more primitive or embryonic cells and in which adult functions are absent or diminished. A malignant lymphocyte, for example, would not retain the capacity to fight infections. Anaplastic cells also lack orientation with respect to the parent tissue; instead of an orderly spatial arrangement, their distribution is often jumbled.

Metastasis is the ability of a malignant cell to detach itself from a tumor and establish a new tumor at a remote site within the host. This ability reflects both the lessened cohesiveness of cells within a tumor and the capacity of malignant cells to sustain themselves while floating freely in the blood stream or lymph ducts. Unmetastasized tumors can frequently be removed by surgery or irradiation, but there is much less prospect of treating metastasized malignancies.

Cancers are generally not, in themselves, fatal; that is, with rare exceptions, they do not produce toxins or otherwise kill the host directly. Rather, they seem to have a curious priority on nutrients within the host, nourishing themselves at the expense of other tissues. This malnutrition produces a phenomenon called cachexia, the generalized emaciation and ill-health of the host. Cachexia has frequently been considered to be the ultimate cause of death in a majority of cancer patients, but a recent study suggests that many other factors are involved in such cases.

Julian L. Ambrus and his associates at the Roswell Park Memorial Institute, Buffalo, New York, have studied more than 500 cancer deaths at that institution and found that the chief cause of death was infection, which accounted for 36 percent of the deaths and was a contributory factor in an additional 13 percent. Most of these infections were caused by antibiotic-resistant bacteria. The second most important factors were hemorrhaging and blood clots, which together accounted for 18 percent of deaths and were contributory factors in another 43 percent. Other factors included organ failures caused by invasion by cancer cells, 10 percent, respiratory failure, 19 percent, and cardiovascular insufficiency, 7 percent.—T.H.M.