REVIEW ARTICLE

Viruses and Cancer

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■ *The answer to the important question, "Do viruses play a role in human cancer?" is still unknown. Although many scientists think that they may play a role, straightforward attempts to isolate human tumor viruses in animals or in tissue cultures have failed. Possibly the most sensitive test object, newborn human infants, of course cannot be used as test objects, and this may explain the failure to isolate human tumor viruses. At present, it would appear that the best means of tackling the problem of viral-induced carcinogenesis is to study the basic characteristics of known tumor viruses and the basic aspects of their interactions with cells. Both RNA-containing and DNA-containing viruses, two obviously different classes of virus, can cause cancer and therefore both classes must be studied in order to obtain a complete picture of the role of viruses in causing cancer in animals and cell transformation in vitro. Such basic studies already have yielded information of great importance to general biology.*

A number of exciting developments have occurred in the area of virus-induced cancer. One of these is the oncogenic capacity in hamsters of certain human adenoviruses, and an intensive probe of their possible role in human cancer is in progress. Another is the detection by electron microscopy of virus-like particles in the tissues and serum of patients with leukemia.

Rigid criteria have been suggested to establish etiologic significance of viruses recovered from human cancer tissues and of the virus-like particles observed by electron microscopy in serum or malignant tissues from cancer patients.

If viruses are eventually found to play a role in human cancer, then perhaps the disease can be prevented by vaccines and treated with antiviral substances.

THE POSSIBILITY that viruses play a role in the etiology of certain cancers of man has been discussed recently in a number of excellent reviews.[4,26,28,41,44] The purpose of this review will be (1) to outline the factors that have led to the current interest in the virus theory of cancer, (2) to describe the physical and chemical properties of known tumor viruses as well as their ability to cause cancer in intact animals and malignant transformation of cells in vitro, (3) to describe the new developments in the search for human tumor viruses, (4) to discuss the problems of establishing etiologic significance of isolates from human cancer tissue, and (5) to discuss measures that might be useful in the prevention and treatment of virus-induced cancer.

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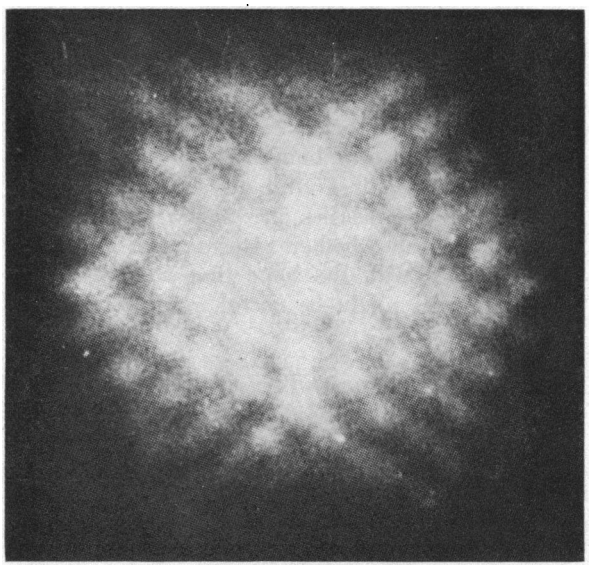

Figure 1.—Electron micrograph that illustrates the cubic symmetry of human adenovirus particle. Courtesy of Dr. R. Horne (J. Mol. Biol. 1:84, 1959).

Historical Background

By the end of the 19th century, several similar theories of the cause of cancer had evolved. These suggested that an internal change took place in the cell that allowed it to escape from the normal growth-regulating mechanisms. In 1903 Borrel[10] proposed the virus theory of cancer. He reasoned that viruses may infect cells and induce a proliferative effect without causing cell death. The resulting virus-cell complex would then multiply indefinitely and induce unregulated cell growth that resulted in cancer. Five years after Borrel proposed his theory, the first tumor virus, an avian leukemia virus, was discovered. Thereafter, a number of other factors, such as chemical carcinogens, genetic background, hormones and x-rays, were found to play an etiologic role in animal cancer. Finally, in one tumor, mammary cancer in mice, it was found that clinical disease results from the interaction of three etiologic factors: genetic background, hormones and a virus.

Ever since Borrel proposed his theory, investigators have searched for viruses in animal and in human cancer material. While those who sought cancer viruses of animals have been highly successful; those seeking human cancer viruses have been unsuccessful. The reason for this discrepancy is unknown; however, investigators dealing with animals could inoculate the cancer tissue obtained from the animals with tumors into animals of the same species, including newborn animals. This technique proved highly successful for the isolation of animal cancer viruses. Obviously such a technique would not be justifiable in human newborns for although human cancer material has been inoculated into human beings, these have, in general, been elderly persons who already had some form of malignant disease.

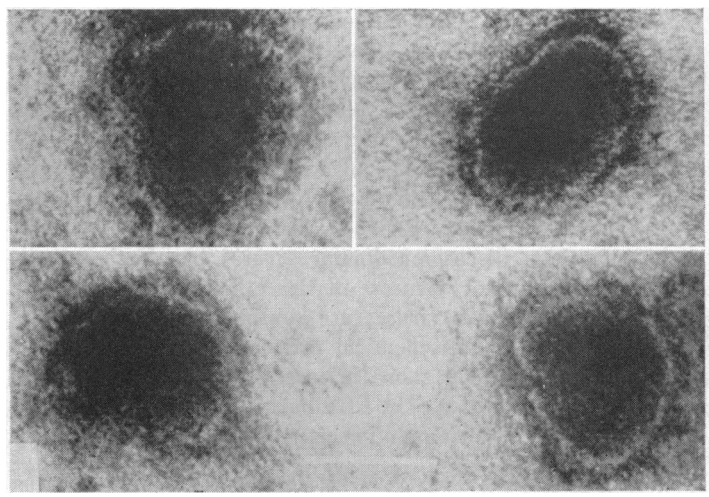

Figure 2.—Electron micrograph that illustrates the helical symmetry of avian myeloblastosis virus particles. Courtesy of Dr. K. O. Smith (J. Nat. Cancer Inst. 33:557-570, 1964).

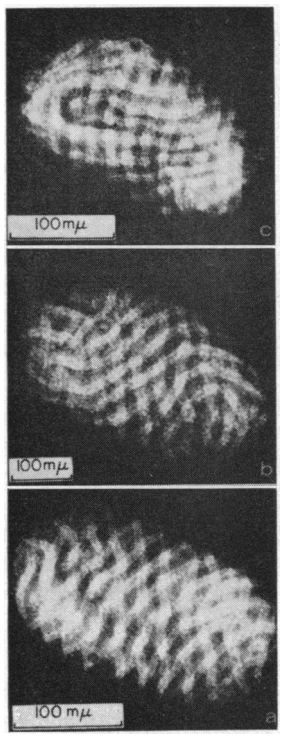

Figure 3.—Electron micrograph that illustrates the complex symmetry of orf virus particle. Courtesy of Dr. J. Nagington (Virology, 23:461-472, 1964).

Why Are More Investigators Currently in Quest of Human Cancer Viruses than Ever Before?

In view of the multiple factors that can cause cancer and the failure to find human cancer viruses, one might wonder why interest in the virus theory has had a major revival. First, an ever-increasing number of animal cancers have been discovered to be a response to a virus infection.[26] These include the avian and murine leukemias, rabbit papilloma-carcinoma, rabbit fibroma and myxoma and murine mammary carcinoma. Bovine ocular carcinoma, canine mast cell sarcoma and sheep adenomatosis are less definitely associated with viral infections. In addition, certain viruses (polyoma virus of mice, SV40 of monkeys and adenovirus types 3, 7, 12 and 18 of man)* can induce cancer in certain rodents, but what, if any, oncogenicity properties they have in the host of origin is unknown at present. Second, virus-like particles have been demonstrated by electron microscopy in precancerous and cancerous tissues of man[16] and in the serum of patients with leukemia.[2,11,15,39] Third, the arbitrary categorization of viruses into two groups, acute infectious disease-producing viruses on the one hand and tumor viruses on the other, is no longer tenable. Tumor viruses are similar to other viruses in physical and chemical properties, in the type of effect they can cause in infected cells and in mode of transmission. The fifth basis for interest in viral etiology of human cancer lies in certain epidemiologic data. The most interesting example is Burkitt's African lymphoma, which affects children of both sexes and several races in Africa and New Guinea.[12] The lymphoma is geographically limited in occurrence to areas in which the climatic conditions favor continuous breeding of mosquitoes, and it has been suggested that the tumor may be caused by a mosquito-born virus, much as rabbit myxomatosis and rabbit fibromas are caused by viruses that are spread by mosquitoes. Additional epidemiologic evidence is the observation of clusters of cases of human leukemia,[24] the development of tumors after smallpox vaccination, after herpes simplex and herpes zoster infection, and the development of testicular tumors after mumps and rubella orchitis.[26] The sixth basis is the increasing amount of funds that have become available for biological research, including cancer research. Stimulated in part by the isolation of polioviruses in tissue culture and the subsequent development of the poliovaccines, other viruses have been sought for and isolated in tissue culture systems. These include the viruses that cause German measles and the common cold (53 virus serotypes have been isolated to date) that could not be isolated in experimental animals or in embryonated eggs. Seventh, the success now being achieved in the field of prophylaxis against viral diseases, for instance poliomyelitis and measles, provides a potent stimulus to determine whether viruses play a role in human cancer with the hope that vaccines made of such viruses might be useful in the prevention of cancer.

What Do Known Tumor Viruses Look Like and of What Are They Composed?

Tumor viruses are not all alike but differ considerably from one another in physical and chemical properties. As do all known viruses, tumor viruses have one of three types of physical structure: cubic symmetry, helical symmetry or complex symmetry. Figures 1 to 3 illustrate these three types of symmetry. The chemical components of all known viruses consist of nucleic acids, either desoxyribonucleic acid (DNA) or ribonucleic acid (RNA) and protein. In addition, some viruses contain lipid. Table 1 summarizes the physical and chemical properties of the known tumor viruses. Several points concerning the nucleic acids of the viruses on this table are of interest. It is presumed that it is the genetic material—that is, the nucleic acid rather than the protein or the lipid component of the virus particle—which is responsible for inducing the neoplastic transformation in the infected cell.[17,44] Although there is no direct evidence in support of this for any RNA-containing virus, it has been shown that DNA extracted from rabbit papilloma virus can initi-

*References: 17, 18, 20, 27, 29, 42, 43, 45.

ate tumors[31] and that the transforming activity of polyoma virus requires DNA-containing particles and not empty protein shells devoid of nucleic acid.[1] The DNAs extracted from adenovirus types 12 and 18, from Shope papilloma and from polyoma have similar densities when centrifuged to equilibrium in cesium chloride.[21] This finding suggests that the proportion of the four nucleotides forming these DNAs is similar. The DNA of polyoma has the same double-stranded configuration as cellular DNA,[13] and it recently has been shown that certain regions of polyoma viral DNA and mouse cellular DNA are homologous—that is, the sequence of the nucleotide bases is similar.[6] Polyoma-induced mouse tumor cells contain DNA with even larger regions of homology—that is, genetic relatedness—for polyoma viral DNA. The DNA-containing tumor viruses (Shope papilloma, polyoma, SV40, adenoviruses) have been termed "hit and run" viruses because following infection and malignant transformation of cells, no infective virus can be detected. However, the presence of noninfectious viral genes in such cells is indicated by the appearance of viral antigen in the transformed cell.[17,30] Obviously the findings of DNA homology bear directly on the important question of how "hit and run" viruses induce genetically stable malignant change in cells and leave their antigenic "fingerprint" in the cells.

The polyoma virus, SV40 and human adenoviruses are tumor viruses of interest in that their oncogenic potential in the host of origin, namely, the mouse, monkey and man, is unknown. However, they can induce tumors when inoculated into hamsters.* These data suggest that intensive studies should be made of human tumors to seek traces of adenoviral DNA or antigens or both.

In summary, the known tumor viruses fall into three main groups when classified according to physical and chemical properties (Table 1) but, except for their demonstrated oncogenic potential, are not otherwise different from nononcogenic viruses.

*References: 17, 18, 20, 27, 29, 42, 45.

TABLE 1.—*Physical and Chemical Properties of Known Tumor Viruses*

Type Symmetry	*Nucleic Acid*	
	RNA	*DNA*
Cubic	No viruses	Shope papilloma, polyoma, SV40, adenovirus types 3, 7, 12, 18, human wart
Helical	Avian and murine leukemias, rous sarcoma, murine mammary carcinoma	No viruses
Complex	No viruses	Shope fibroma, yaba, molluscum contagiosum

What Effects Do Tumor Viruses Produce When Inoculated Into Experimental Animals?

Tumor viruses can induce neoplastic lesions, malignant or benign, in appropriate experimental animals, especially newborn animals. In some instances, the incubation period between inoculation of virus and the appearance of the tumor may be many months. Such a prolonged incubation period, if translated into terms of human life, would be many years.

Figure 4 illustrates tumors induced by avian myeloblastosis virus. In addition to visceral lymphomatosis illustrated here, the chicken leukosis viruses can induce other malignant neoplasms such as leukemia and kidney tumors similar to human Wilms' tumor.[25] They also can induce certain benign neoplasms such as hemangiomas and periosteal hyperplasia.[8]

Polyoma virus also can induce a number of neoplasms in the mouse, hamster, rabbit and rat that range from hyperplasia of the renal tubules to malignant metastasizing osteogenic sarcomas.[42,43] Figure 5 illustrates renal angiosarcoma in the hamster induced by this virus. Figure 6 illustrates the undifferentiated malignant tumors induced at the site of inoculation of human adenovirus type 12.

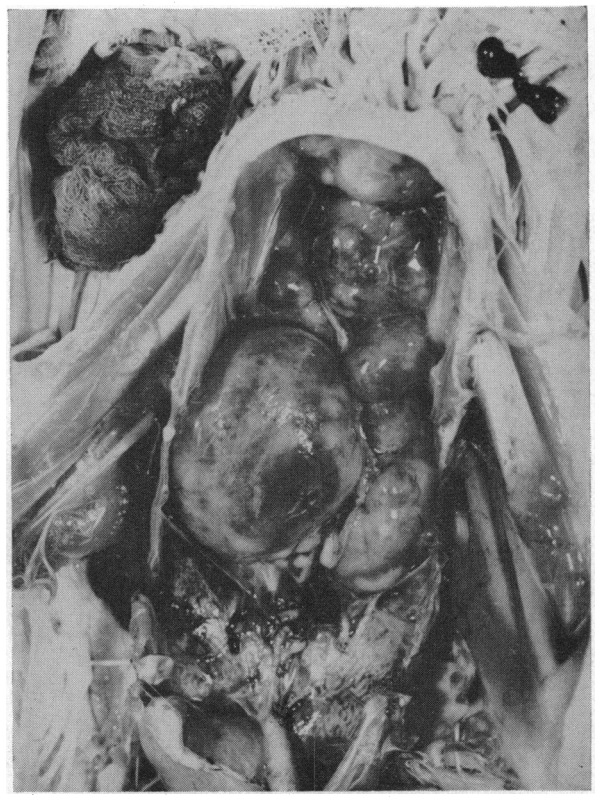

Figure 4.—Photograph of abdominal cavity of adult chicken showing tumors induced by avian myeloblastosis virus. Courtesy of Dr. M. Baluda.

Other human adenoviruses, types 3, 7, and 18, can induce similar tumors in hamsters.[20,27,29]

In addition to their oncogenic effects, certain tumor viruses can induce non-neoplastic diseases in animals. For instance, Rous sarcoma virus can induce hemorrhagic necrosis of the liver and kidneys of chicken. Polyoma virus can induce pneumonitis in mice and Shope papilloma virus can induce cellulitis in the skin of the rabbit.

In summary, tumor viruses can induce non-neoplastic as well as neoplastic diseases in experimental animals. In some cases, the incubation period between virus infection and tumor can be quite long. Certain tumor viruses (polyoma, SV40, human adenoviruses) are capable of inducing cancer in experimental animals but their role in producing cancer in the host of origin is unknown at present.

What Effects Do Tumor Viruses Have Upon Cells Infected in Vitro?

As has been observed for all known viruses, certain tumor viruses can cause cytocidal effects, including intranuclear and intracytoplasmic inclusion bodies in cells infected in vitro. Other tumor viruses, such as the avian and murine leukemia viruses, do not cause cytopathic effect in cells in vitro.

Fortunately it was discovered recently that viral-induced neoplastic changes could be reproduced in isolated cells in tissue culture. This in-vitro carcinogenesis, so-called cell transformation, has been observed with six viruses: Rous sarcoma virus (RSV), polyoma, avian myeloblastosis virus, SV40, bovine papilloma virus and adenovirus type 12.[34,44] It is of interest that no other carcinogen, x-rays, chemicals or hormones can induce such cell transformation in vitro. Figure 7 illustrates the focus of transformed cells infected with Rous sarcoma virus. The cells on the periphery of the focus are normal chick fibroblasts which grow in a monolayer in the culture vessel and because of a phenomenon called "contact inhibition," do not form piles or foci of multilayered cells.[38] Infection of chick cells by Rous sarcoma virus induces a transformation of the cell morphologic structure and physiologic state, and a loss of contact inhibition permitting the cells to pile on top of one another. Recently it has been found that Rous sarcoma virus is a "defective virus."[23] That is, it cannot complete its infective cycle and produce mature infective virus

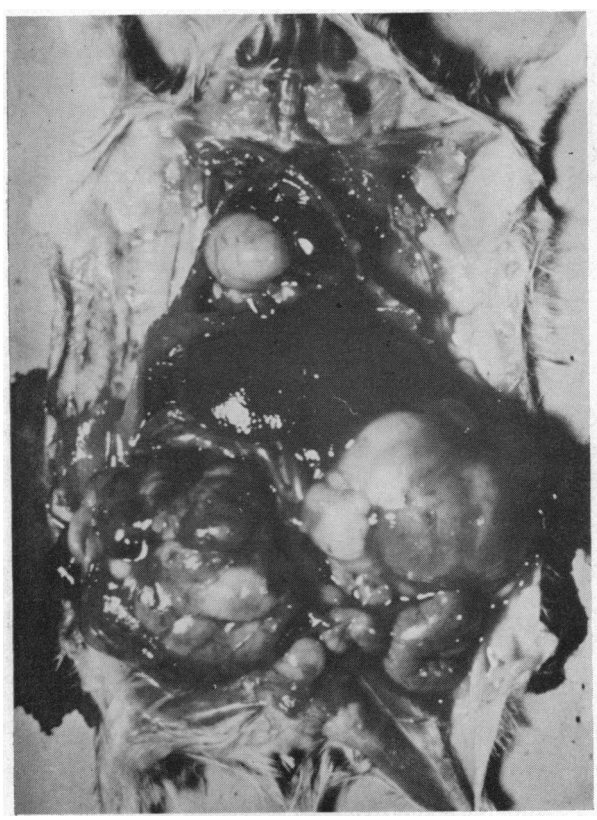

Figure 5.—Photograph of hamster showing tumors induced by polyoma virus. Courtesy of Dr. B. Eddy.

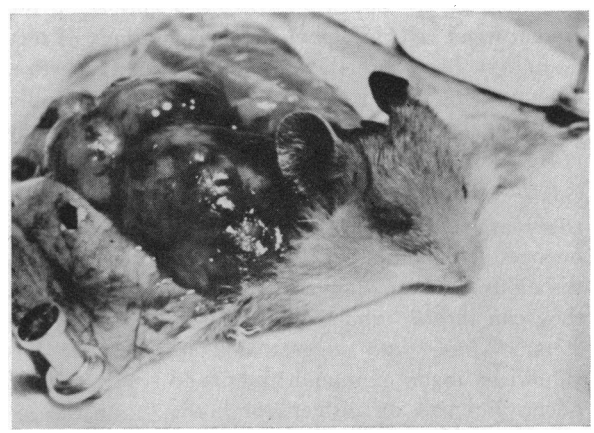

Figure 6.—Photograph of hamster showing tumors induced by adenovirus type 12. Courtesy of Dr. R. Huebner.

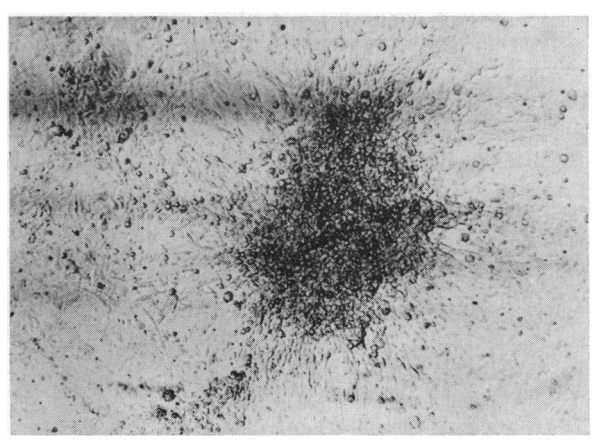

Figure 7.—Photograph of chicken embryo cells showing a focus of cells rendered malignant by Rous sarcoma virus. Courtesy of Dr. H. Rubin.

particles unless a second or "helper" virus has infected the same cell and initiated or induced the production of proteins. The viral-induced proteins of the "helper" virus are used by the Rous virus to form its protein coat.

Cells transformed by Rous sarcoma virus, an RNA virus, continue both to multiply and to release infective RSV (in the presence of the "helper" virus) over long periods.[44] In contrast, cells transformed by DNA viruses (polyoma, SV40, adenovirus 12) continue to multiply but do not yield infective virus. At present, no reports of "helper" viruses for DNA tumor viruses have appeared, and it has not been possible by any means (x-rays, ultraviolet light, chemical carcinogens, cortisone, starvation) to induce cells transformed by these viruses to produce infective virus.[6,17,46]

If, however, such transformed cells are inoculated into appropriate host animals (mice or hamsters), they can induce tumors, and in addition, antigenic "fingerprints" of the virus can be detected in the transformed cells.[17,22,30]

In summary, certain tumor viruses can cause cytopathic effects as well as malignant transformation of cells infected in vitro. Intensive studies of cell transformation suggest that in certain systems the ability of a virus to cause malignant transformation is actually linked to its inability to complete its reproductive cycle. Part of the viral genetic material that can be detected as viral antigen remains in the transformed cells and is passed from generation to generation. These findings apparently support Borell's concept of a virus-cell complex that could induce cancer.

How Are Tumor Viruses Spread?

As is true for all known viruses, tumor viruses are spread by three fundamentally different methods.[28] One method, horizontal spread, is transmission of virus within a species by postnatal contact. Rous sarcoma virus, polyoma, SV40, adenoviruses and avian leukosis viruses are spread in this manner. The second method, vertical spread, is prenatal or neonatal transmission of virus within a species from mother to young. Ordinary viruses, such as human cytomegalovirus, rubella and the Coxsackie B group are spread in this manner as are the avian and murine leukemia viruses. The third method, exogenous spread, is transmission of viruses from one species to another with or without the aid of insect vectors. In tumor viruses the rabbit fibroma and myxomatosis viruses are spread by arthropod vectors.

In summary, as with other viruses, tumor viruses are spread by means of horizontal, vertical and exogenous transmission.

What Are the New Developments in the Search for Human Tumor Viruses?

First, a number of authors have reported isolation of viral agents from human cancer tissues. Dalldorf and Bergamini[14] and Bell and coworkers[9] have reported the isolation of viral agents from Burkitt's tumors; Negroni[35] has recovered agents from leukemic tissues, and Sohier and coworkers[40] and McAllister and his associates[33] have recovered adenoviruses from solid tumors. All of these agents were detected because of their ability to cause cytopathic effects in tissue cultures. The isolation of these viruses from human tissue raises the important question of their significance—whether they played an etiologic role in the cancer, whether they were "passenger" viruses latent in the tumor tissue or whether they were laboratory contaminants. McAllister and coworkers[33] applied certain criteria for determining the significance of their isolates, and the results of these experiments did not indicate with certainty whether or not the viruses had etiologic significance. The problem of establishing etiologic significance of viruses isolated from cancer tissues will be discussed below.

Second, Epstein and coworkers[19] reported the possible induction of bony changes suggestive of Burkitt's tumor in monkeys following injection with extracts of Burkitt's tumor tissue. This exciting observation would suggest that Burkitt's tumor is induced by a virus and that it is the first known human cancer virus that will cause tumors in laboratory animals. Recently, however, the diagnosis of the bony changes induced in the monkeys has been challenged. The bony dysplasia observed may simply be due to a nutritional deficiency of captive monkeys and not due to neoplasia. At present, therefore, the reported transmission of Burkitt's tumor to monkeys is not an established fact.

Finally, as mentioned above, intense interest surrounds the reports of virus-like particles observed by electron microscopy in the serum of leukemic patients.[2,11,15,16,39] These particles resemble the myxovirus-like particles of avian and murine leukemia and therefore could represent their human leukemia counterpart.

However, in order to put the human particles in perspective with the known leukemia viruses, the methods of detection of the latter are summarized in Table 2.

All avian and murine leukemia viruses can induce leukemia in vivo and can be observed by electron

TABLE 2.—*Detection of Known Leukemia Viruses*

1. Induction of leukemia in vivo
2. Tissue culture effects
   a. Malignant transformation of infected cells
   b. Viral interference
   c. Helper virus effect
   d. Viral antigen in infected cells
3. Electron microscopic observation of virus particles in tissues and in serum

microscopy. Also the presence of viral antigen in cells infected by Rous sarcoma virus or by Friend murine leukemia virus has been demonstrated by fluorescent antibody.[47] In addition, viral antigen has been detected by complement fixation reaction in cells infected with Rous sarcoma virus or avian leukemia viruses.[5] On the other hand, only avian leukemia viruses have demonstrated the "helper" virus[23] and interference effects[37] (for Rous sarcoma virus) and only one of the avian leukemia viruses, avian myeloblastosis virus, can induce malignant transformation of infected cells.[7]

In contrast to these data, to date the human particles have not been adequately tested for their capacity to induce leukemia in any experimental animal or to induce tissue culture changes of any type. Accordingly, the significance of these particles must be viewed skeptically until more is known about them. This position is perhaps fortified by the fact that it has not been clearly established that the particles do not represent cellular debris or pleuropneumonia-like organisms (PPLO) both of which may be present in the serum of leukemic patients and could resemble myxovirus-like particles when observed in the electron microscope.

In summary, although viruses have been isolated from human cancer material and virus-like particles have been observed in the serum of leukemic patients, the significance of these observations is at present unknown.

What Evidence Is Required to Establish an Etiologic Relationship Between a Virus and a Neoplasm?

This problem has been discussed by a number of authors[3,32] and it is perhaps the most difficult problem in cancer biology. It is known that tumor tissue may harbor not only the specific etiologic agent but also passenger viruses which can include tumor-producing and non-tumor producing viruses. For instance, certain leukemic tissues of mice contain the Gross virus (specific etiologic agent) as well as the polyoma virus (passenger tumor virus). Thus rigid criteria must be satisfied before a causal relationship between an isolated virus and a neoplasm can be accepted. A summary of the suggested criteria is as follows:

1. Isolation from tumor tissue of a virus that can induce tumors in vivo or cell transformation in vitro.

2. Repeated isolation of the virus from individuals with the same tumor type.

3. Demonstration of neutralizing antibody to the virus in the serum of the patient, and also determination of the distribution of neutralizing antibody in the human population and its quantitative relation to the distribution of the specific neoplastic disease. Failure to detect neutralizing antibody would not exclude the virus as a causative agent because in experimental animals some known tumor viruses have failed to form antibodies in their natural hosts[38]; however, such an unknown virus might produce antibodies in another species, and repeated isolation of a virus with the same serotype from patients with the same tumor type would suggest an etiologic relationship.

4. Demonstration of viral antigen ("fingerprint") in tumor cells. In view of the studies of Huebner and coworkers,[30] the antigen of certain DNA-containing tumor viruses may be detected in tumor cells even though infective virus is not present. This observation may provide a new tool in the search for tumor viruses.

5. Suppression of incidence of a tumor by vaccination with the viral antigen.

6. Finally, the induction of cancer in inoculated human volunteers would prove the etiologic role of a viral agent beyond doubt. It is possible that such an experiment could be avoided if the other criteria were fulfilled.

It is obvious that in order to establish a firm etiologic relationship between a virus and a tumor, more evidence is required than mere isolation of an infective virus from tumor tissue or detection by electron microscopy, of virus-like particles in human serum (whose infectivity is unknown).

How Would the Discovery of Human Cancer Viruses Be Helpful in the Treatment and Prevention of Human Cancer?

If human cancer viruses are eventually discovered and if they are typical viruses and the cancers they induce are typical cancers, one might ask how can these data be put to use?

First, can virus vaccines be used to control human cancer as they have certain virus diseases? Even if viruses are isolated and accepted as human cancer viruses according to the criteria discussed above, this question may require many years to answer. Ecologic information about them must be gathered, such as prevalence, age distribution, modes of spread, infectious cycle and possible reservoirs. In the meantime a vaccine prepared from the virus and administered to human beings may require decades to evaluate. For instance, if adenoviruses (in the presence of certain cocarcinogenic factors, such as chemicals, hormones or x-rays) induced certain solid tumors and if the latent period between virus infection and tumor were 50 or more years, it is obvious that the results of a vaccine trial might require five decades or more. On the other hand, if viruses induce childhood leukemia (and are not transmitted congenitally), the protective effects of a hypothetical vaccine might be evaluated in a few years.

Finally, one might ask: Will viral inhibitory substances effective in the prevention and treatment of virus diseases be effective in the prevention and treatment of virus-induced cancer? At present only three substances have proven antiviral activity—adamantanamine hydrochloride (used in prevention of influenza A virus infections), thiosemicarbazones (used in prevention of smallpox) and 5-iodo-deoxyuridine (used in treatment of herpes keratitis).[36] If more antiviral substances are developed, it is possible that some of them might be effective in virus-induced cancer. In addition, careful studies of the effects of antiviral substances in cells infected by tumor viruses might yield information that will aid in developing a rational cancer chemotherapy.

Other Dividends Obtained from Studies of Tumor Viruses

The 1964 Lasker Awards for basic medical research were made to Dr. Renato Dulbecco of the Salk Institute for Biological Studies at San Diego and to Dr. Harry Rubin of the University of California, Berkeley, for studies of tumor viruses.[17,38] The research of these two distinguished California scientists on polyoma virus (Dulbecco) and avian leukemia and Rous sarcoma viruses (Rubin) clearly demonstrated the far-reaching biological significance of the studies of tumor viruses. Dulbecco recognized that viral-induced transformation of cells not only is a form of experimental carcinogenesis but also can be a form of cellular differentiation, the "understanding of which is one of the major objectives of biological research." Rubin's studies of vertical and horizontal transmission of avian leukemia viruses provide an important model for use in studying the epidemiology of leukemia in man as well as the epidemiology of other viral diseases such as serum hepatitis. In addition, his discovery of a "defective" animal virus (Rous sarcoma virus) opens an entire new dimension in animal virology.

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