

A Survey of the Tumor Virus Problem from an Epidemiologic Standpoint

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SUMMARY

This presentation represents an attempt to synthesize current knowledge of oncogenic viruses from the viewpoint of the epidemiologist faced with the problem of testing hypotheses on the relationship of viruses to human cancer. In particular, the need for considering models of the pathogenesis of the infection is stressed.

In some respects the history of tumor virology reads like the case history of a manic-depressive psychosis: great cycles of energy and productivity alternating with withdrawal and discouragement. However, to many persons, this case history may resemble more that of a schizophrenic, where out of a massive flow of words and ideas it is difficult to synthesize a coherent picture and to sift out the meaningful from the imaginary. Regardless of the diagnosis, it is apparent that our patient is to be reckoned with; at all levels of cancer research, from the biochemical to the epidemiologic, it is necessary continually to keep in mind the possible participation of viral agents in the biologic system under study. There are several reasons for this: the subtlety and variety of viral influences on cells; the virtual impossibility of proving the absence of a viral influence; and the increasing number and diversity of known viruses detectable only by indirect and specialized technics, which can be extrapolated to mean that there must exist many more even subtler agents not detectable by present procedures.

The purpose of this presentation is to try to do a little sifting, to give a concise summary of those aspects of tumor virology which seem most pertinent to the problems of the epidemiologist, and to discuss these problems in terms of several questions facing the epidemiologist who is attempting to elucidate the etiology of tumors.

Our thinking on the over-all approach to studying viral etiology of cancer has changed markedly in the past few years. The traditional goal has been to isolate a virus from a tumor and to let the etiologic implication depend on the frequency with which the virus can be recovered from tumors, as compared with control tissues, and on the similarity of tumor type produced in laboratory systems to that from which the virus was recovered. Several observations have forced revision of this line of thought—particularly the findings that polyoma virus acts in many respects like nontumorigenic cytolytic viruses (8), the dissociation between time of maximal virus growth and time of tumor response in polyoma infection (30), and the oncogenicity of several adenoviruses (22, 33).

These findings indicated for the first time that there is no sharp distinction in general properties between tumorigenic and nontumorigenic viruses—that, indeed, viruses of acute infectious disease may be tumorigenic under certain circumstances, and that a tumor may be a late sequel of an acute infectious process and may not contain the virus. Thus, the floodgates have been opened; we no longer lack candidate viruses to consider as possible tumorigenic agents but must at least keep an open mind towards every virus.

It is only too clear that oncogenicity for an experimental animal does not prove that a virus is oncogenic in its natural occurrence; such proof can only be obtained by epidemiologic technics, which involve testing hypotheses of the relation of particular viruses to particular tumors.

What etiologic hypotheses should the epidemiologist consider testing? This is a most difficult question to answer in realistic terms. There is no *a priori* basis for rejecting the possibility that any conceivable virus is the causative agent of some particular tumor, provided there is a possibility for the virus to have gained access to that tissue. Thus, the number of conceivable hypotheses of the relation of particular viruses to particular types of tumor is so immense that we must somehow make judgments of most likely hypotheses based on whatever generalizations we can extract from known systems in lower animals. Stated in another way, we should like to know what characteristics of a virus give us information as to whether it is a likely or an unlikely candidate for tumorigenicity in its natural occurrence.

First, let us list the model systems from which we must seek our generalizations. In Table 1 the most important known tumor viruses are listed, along with a tentative classification of their known tumorigenicity—whether it occurs in nature or is only known as an artificial laboratory phenomenon, and whether virus replication can occur independent of tumor response (facultative tumorigenicity) as opposed to the situations in which virus is liberated only by tumor cells (obligate productive tumorigenicity) or in which tumor development is the only

TABLE 1
CERTAIN CHARACTERISTICS OF TUMOR VIRUS INFECTIONS

| Taxonomic group | Virus | Host | Tumorigenicity |
|-----------------|--|--------------------------|--------------------------------------|
| Papovavirus | Polyoma | Mouse | (Natural), facultative |
| | | Hamster, Rat, etc. | Artificial, obligate-nonproductive |
| | Bovine wart | Cow | Natural, obligate-productive |
| | Rabbit wart | Horse, hamster | Artificial, obligate-nonproductive |
| | | Cottontail rabbit | Natural, obligate-productive |
| Adenovirus | Adenoviruses 12, 18, 7 | Domestic rabbit | Artificial, obligate-(nonproductive) |
| | | Monkey | |
| | | Hamster | Artificial, obligate-(nonproductive) |
| Poxvirus | Rabbit fibroma Squirrel fibroma Yaba | Human | |
| | | Hamster, mouse, rat | Artificial, obligate-nonproductive |
| | | Rabbit | Natural, obligate-productive (?) |
| | | Squirrel | Natural, obligate-productive (?) |
| Myxovirus-like | Mouse leukemia | Monkey | Natural, obligate-productive (?) |
| | | | |
| | Fowl leukosis | Mouse | Natural, facultative (?) |
| | | Rat | Artificial, facultative |
| | Mouse mammary | Chicken | Natural, facultative |
| | | Hamster, guinea pig, rat | Artificial, obligate-(nonproductive) |
| | | Mouse | Natural, facultative |

response and infectious virus is not liberated at any time (obligate nonproductive tumorigenicity). This type of classification may be useful in stressing how much of our knowledge is based on artificial systems which often do not reflect the epidemiologically important characteristics of the natural situations and in emphasizing the fact that, in its present usage, the term "tumor virus" means only an agent that under some particular unique set of conditions may induce tumors, regardless of whether it does so in its natural occurrence.

Is there any distinguishing characteristic of all, or even some, of these viruses which sets them apart from "non-tumorigenic viruses"? Such common denominators could be looked for in the structure, chemical composition, laboratory characteristics, epidemiology, etc. First, even membership in a particular virus group does not guarantee that a virus is or is not tumorigenic. Known tumorigenic viruses fall into at least 4 major virus families, but in none of these groups is every member known or suspected to be tumorigenic. For example, the papovavirus group (26), which includes polyoma, SV40, and the papilloma viruses, also includes 2 apparently nontumorigenic viruses—mouse K virus and the rabbit kidney-vacuolating virus. Among the adenoviruses, tumorigenicity appears not only to be restricted to certain serotypes, but in the case of Type 7, to be limited to certain strains within the type (12). To date, no tumorigenicity has been detected with any picornavirus, arbovirus, nitavirus, or reovirus, although the possibility of tumorigenic potential of reoviruses has been suggested by their close similarity in structure and chemical composition to the wound tumor virus of plants (13).

It is apparent that, as a whole, there is no common denominator with respect to structure or chemical com-

position. The papova- and adenoviruses are DNA-containing,¹ nonmembranous, non-lipid-containing viruses with cubic symmetry; the poxviruses contain DNA; and the myxovirus-like agents are RNA viruses consisting of a helically wound internal nucleoprotein component covered by a lipid-containing protein envelope. Papovaviruses and adenoviruses replicate in the nucleus and poxviruses, in the cytoplasm; the myxovirus-like viruses assemble at cell surfaces. At a finer level, however, there may be important and useful markers, i.e., in the composition and structure of the viral nucleic acid, at least in the case of the DNA viruses. The DNA of tumorigenic papovaviruses and adenoviruses shows base composition closer to that of mammalian cells than does DNA from nontumorigenic viruses, including nontumorigenic adenoviruses (14). While this type of study has been done with only a very limited number of viruses and cannot be regarded as a valid generalization, the implication of homologous regions in viral and host DNA fits so well with current thinking about the molecular basis of viral neoplasia that there is great hope for important predictive information from this approach. Another possibly important and unique feature is the ring structure of polyoma virus DNA (6); however, so little information is available on the tertiary structure of other viral nucleic acids that this finding can be considered only a possible lead.

The question of general laboratory characteristics as an indication of possible tumorigenicity of a virus is one that has undergone immense change in the last decade. Ten years ago one might have felt that if a virus is not able to be handled by standard laboratory procedures, if it cannot be propagated *in vitro*, if it won't do anything

¹ The abbreviations used are: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; CF, complement fixing.

that you want it to do, then it probably is a tumor virus. Fortunately, this generalization has passed into oblivion. Many tumor viruses, both natural and artificial, can be handled by standard laboratory technics. Many propagate in tissue culture, some hemagglutinate, and many are sufficiently antigenic that serologic technics can be applied to their epidemiology.

The ability of tumor viruses to initiate malignant-appearing proliferation of tissue culture cells ("transformation") (5) may be a highly important common denominator among tumor viruses, and may also be an important method for detecting candidate tumor viruses. Polyoma, SV40, rabbit and bovine papilloma, adenovirus 12, and several strains of avian leukosis viruses produce *in vitro* transformation. However, there is insufficient evidence as yet to assess the degree of correlation between transformation and tumorigenicity. Thus, SV40 transforms mouse and rabbit cells but is not tumorigenic for these species *in vivo*; on the other hand, essentially no nontumorigenic viruses have been tested for transforming capacity.

Another marker that has been considered is the ability of a virus to produce chromosomal derangements in acutely infected cells. Rous sarcoma virus is reported to produce this effect (25), as do 2 nontumorigenic viruses, herpes simplex (18) and measles (27). However, although chromosomal derangements are very common in virus-transformed cell lines, they often appear to develop subsequent to the morphologic changes in the cells (4).

Concerning epidemiologic patterns of tumor virus infection, there is clearly no common denominator. Polyoma virus spreads by contact with infected urine; fowl leukosis and probably mouse leukemia viruses are transmitted transovarially or possibly in the latter case, transuterinely; the mouse mammary agent and laboratory strains of mouse leukemia viruses are milk borne; the mammary agent can also be transmitted venereally; fibroma virus is mosquito borne; and wart viruses are probably spread by fomites.

What attention should be paid to viruses of other species as possible carcinogens in man? For many years it was a dictum of cancer virology that tumor viruses are highly species specific, but there are now many exceptions. Papovaviruses of mouse, monkey, and bovine origin induce sarcomata in hamsters and other rodents, and the bovine virus, in the horse as well; adenoviruses 12 and 18 produce a characteristic type of tumor, considered to be an embryonal carcinoma or malignant mesothelioma, in hamsters, rats, and mice; and one strain of Rous virus induces connective tissue tumors in rats, mice, hamsters, monkeys, and other mammals. Two characteristics of these cross-species systems are of importance for the epidemiologist. In most such systems, tumor response occurs only as a local response to a large virus input, which could occur with virus-contaminated vaccines; and secondly, the fact that the tumors are likely to be noninfectious would greatly complicate etiologic studies. In this connection it should be stressed that contamination of vaccines by tumorigenic viruses is a reality, SV40 virus in polio and adenovirus vaccines being the prime examples. In addition, any egg-grown vaccine would

almost certainly contain avian leukosis virus, and it is by no means certain that present methods of testing for leukosis virus contamination are adequate to exclude all strains.

Another way of viewing the problem of narrowing down the number of hypotheses worth testing is to look for generalizations concerning the tumors in known virus-tumor systems. Are there unique properties of viral tumors that would have value in predicting which human tumors should be studied? First, it is obvious that pathologic type is of great importance for selecting the most probable tumors, by simple analogy with the model systems. Since leukemia in chickens and mice is so clearly of viral etiology, the probability of the same in man appears very great. Likewise, papillomas, mammary tumors, fibromas, and sarcomas would be judged high in priority. However, when one considers the great range of types of malignancy induced by polyoma virus and various fowl leukosis viruses, it is apparent that any tumor type can be considered a candidate for viral etiologic studies. At the histologic level, there does not seem to be any distinguishing feature, such as inclusion bodies, inflammatory reaction, type of necrosis, etc. Even at the level of electron microscopy, there is no reliable guide; obviously, finding viral particles in association with a malignant disease, as has been done with leukemia in man, raises suspicions of viral etiology, but failure to find viral particles does not preclude it.

Also, it is clear that implication of other etiologic factors, such as genetic influence or carcinogens, does not rule out viruses as a contributing cause. The major importance of genetic factors in determining tumor development in mouse leukemia and mammary tumors, in which viruses are also involved, is familiar to all. Unfortunately, there still is relatively little information available on the interplay between viruses and carcinogens.

The interactions that have been described can be viewed as falling into 3 rather loose categories: (a) synergistic effects between a tumor virus and a carcinogen under definite experimental conditions, such as dual administration of tar and rabbit papilloma virus (29) and the increased susceptibility of X-irradiated adult mice to polyoma tumorigenesis (24); (b) enhancement of the action of a carcinogen by ordinarily "nontumorigenic" viruses, such as the effect of vaccinia infection on methylcholanthrene- and cortisone-treated mice (7); (c) enhancement by a carcinogen of the tumorigenicity of a pre-existing subclinical tumor virus infection, which is often referred to as "activation of a latent tumor virus." The latter is a most important concept, but it is important to stress that it is not based on a solid background of experimental data and that its meaning has not been formulated precisely. The general meaning of the term is that a pre-existing virus is stimulated to exert carcinogenic effect, but this could mean at least 3 things: derepression of genetic activity of an integrated viral genome so that it produces biochemical abnormality in the same cell in which it was previously nonfunctional; induction of an integrated viral genome so that virus is liberated to parasitize other cells, such as may be the case with recurrent herpes simplex; or depression of host

virustatic mechanisms, such as antibody and interferon action, so that a localized chronic productive infection is allowed to disseminate. The latter situation may be exemplified by cytomegalovirus infection.

Recent findings on the antigenicity of virus-induced tumors (16) suggest an additional mechanism which could produce the same apparent phenomenon as effect on the virus itself. These studies indicate that development of a viral tumor is the outcome of the balance between cellular growth rate and strength of a cell-rejection immune response directed against virus-specific antigens in the cell surface; it is thus conceivable that in infected animals there are multiple foci of potential tumors held in check by the immune response and that carcinogens could act either to accelerate the growth rate of these cells or to alter their susceptibility to immune mechanisms. From this viewpoint, the carcinogen could be "activating" the cell rather than the virus.

Possible examples of "activation" of viral tumors are radiation- and chemical carcinogen-induced mouse leukemia, from which leukemogenic viruses may be isolated, and tar- or methylcholanthrene-induced sarcomata in chickens, which have yielded viruses of the leukosis complex. However, until such studies are done prospectively and in relation to the natural history of the viruses in question, their significance remains somewhat obscure, and the mechanisms unknown.

In any event, the recent evidence for integration of genetic material of tumor viruses into host cells has given renewed importance to the concept of viral activation at the cellular level, and studies of the effects of carcinogens on expression of the integrated viral genome may yield results of much importance.

How can we test hypotheses on the etiologic relation of particular viruses to particular tumors? There is no simple answer to this, but perhaps an important part of the answer is a negative statement: we do not test such hypotheses by being bound to Koch's postulates. Scientific proof of an hypothesis consists of elimination of all conceivable and reasonable alternative explanations, not in filling in the blanks in a prescribed set of rules. Koch's postulates are a precise formulation of experimental requirements for eliminating alternative hypotheses in the testing of one particular pathogenetic model, that is, that an infectious agent produces disease reaction during its period of active multiplication. When pathogenesis involves delayed onset of symptomatology, Koch's model just does not apply. Instead, we must formulate or predict the host-parasite relationship we think may obtain, examine this model for what inferences can be made, and then devise means of testing for the expected outcome of those inferences which are unique for that model.

In the known virus-tumor systems there is a variety of host-parasite relationships as indicated by the relation of virus growth and antibody response curves to time of tumor development. Unfortunately, most of these models are based on studies of more or less artificial laboratory systems. The diagrams in Chart 1 portray a number of these patterns. Although time does not permit detailed analysis of the implications of these patterns, several points are evident. First, in the so-called obligate

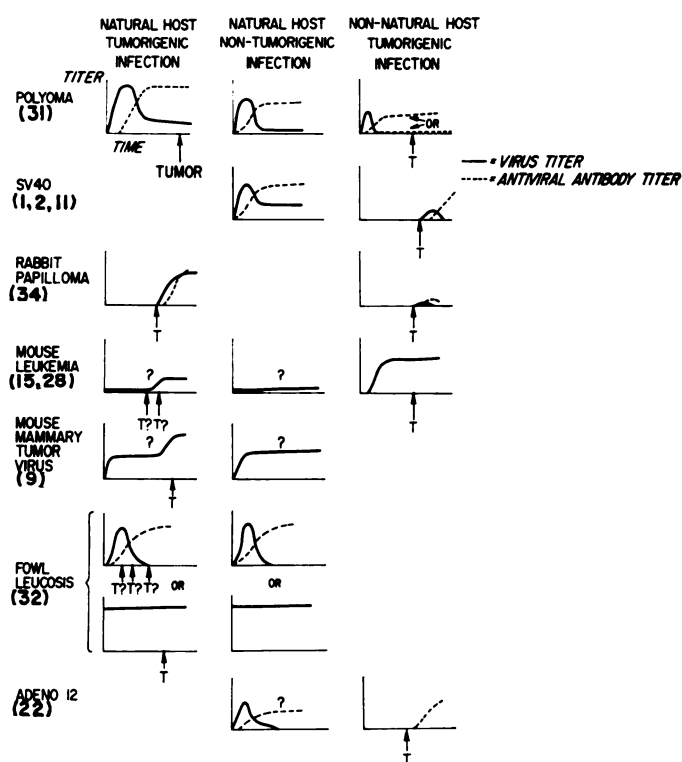


CHART 1.—Diagrams of the pathogenesis of various types of infections with tumor viruses. Numbers in parentheses refer to references.

productive systems, such as rabbit papilloma in the cottontail, Koch's postulates do apply; and if a quantitative factor were introduced, they might apply to the mouse leukemia and mammary agents. Second, there are many systems in which tumors do not yield infectious virus, and Koch's postulates obviously do not apply in these instances. Seroepidemiologic or prospective studies will be necessary to define etiology in such cases. Third, the interrelations of virus, antibody, and tumor occurrence show great variation from system to system, so that no one set of etiologic criteria or experimental design can fit all models; also, it must be remembered that there is variability in details of these patterns among individual animals, which adds a further complexity to epidemiologic studies based on these models. Fourth, these diagrams repeatedly show the contrast between the natural and nonnatural host systems with regard to degree of viral multiplication and persistence.

Polyoma virus infection in the mouse presents a somewhat unique feature for testing etiologic hypotheses. In this system, in which the ratio of subclinical to clinical cases is extremely high, there appears to be a difference in the magnitude of antibody response between the 2 classes of infection (10). Thus, comparison of antibody titers, rather than merely frequency, would be an important part of epidemiologic studies based on this model.

A model system which seems particularly challenging to the epidemiologist is the fowl leukosis pattern seen in Chart 1. In its natural ecology, this virus is transmitted either by transovarian transfer, in which case the offspring may show immunologic tolerance with life-long high-

titered viremia and no antibody response, or by post-hatching contact with infected birds, leading to a more self-limited infection with antibody response (32). Either type of infection may lead to development of leukosis, but the relative risk is not yet known. Given a suspect virus for which laboratory diagnostic tests are available, how can one obtain epidemiologic evidence that a virus with this type of natural history is the cause of a certain tumor? Unfortunately, this question is still academic, since there is no human virus for which we can test that produces a persistent tolerant infection.

The significance of the latent period between infection and appearance of tumor is of great importance for epidemiologic interpretation. In laboratory animal systems this period ranges from 3 days to more than a year, depending on the system and the dosage of virus. Also, with increasing latent period there is marked increase in variability, even between inbred littermates. The mechanism of the latent period is undoubtedly complex, involving an interplay of cell growth and immune rejection, multiple step acquisition of malignancy, repeated carcinogenic insults, etc. However, we are still completely in the dark on the fundamental question of whether a year to a mouse is 1 year or 30 years to a human. Hopefully, the recent development of facilities for the use of infant primates in tumor virus work may help answer this.

The above pathogenic patterns in viral tumors dealt with the classical indicators of virus infection, that is, the detection of infectious virus and of antiviral antibody. However, within the past year an entirely new dimension has been added to the problem of etiologic diagnosis of viral tumors, i.e., the evidence of persistence of the viral genome in virus-induced tumor cells, often with specific modification of the cells due to partial expression of the genome. There are 3 different ways in which persistence of viral genome has been demonstrated. Tumors induced in rodents by adenoviruses (23), SV40 (3), polyoma (17), and fowl leukosis (21) viruses elaborate virus-specific complement-fixing (CF) antigens even though no infectious virus is released; animals bearing these noninfectious tumors may develop CF antibodies which react with the homologous type tumor and, in some systems, with standard viral antigens as well. Second, persistent viral influence has been demonstrated by transplant rejection techniques; animals previously infected with the homologous virus demonstrate a significant degree of resistance against transplanted tumor cells (16). The 3rd technic is essentially a marker rescue experiment, comparable to the phenomenon described with bacteriophage whereby a gene of a defective phage can be incorporated into a superinfecting related phage and thereby rescued from oblivion. This instance is the case of tumors induced by Rous sarcoma virus in chickens and chick embryo tissue culture. Rous virus itself is defective: that is, it cannot carry out all of the steps necessary for synthesis of new infectious virus. However, if cells transformed by Rous virus are superinfected with a related nonsarcomagenic virus of the fowl leukosis group, some of the newly formed virus contains the genetic portion of Rous virus which allows the virus to produce transformation (19).

Aside from their basic biologic implications, these

findings, and particularly the CF antigen studies, have major implications for etiologic studies of tumors. Thus, with the appropriate battery of antisera, it is now possible to obtain definitive etiologic diagnosis of a variety of animal tumors by complement fixation or fluorescent antibody procedures. In adenovirus tumors, the dominant virus-specific antigen, and in SV40 tumors, probably the sole virus-specific antigen, is a virus-induced protein which is not part of the virus particle itself, but rather a component which is tightly bound to cellular constituents in acutely infected cells, and not released in significant quantity into culture fluids (20). These "cell-associated" antigens had not been detected in previous studies of the serologic structure of these viruses, both because of low antibody responses to them in infected or immunized animals and because of the manner of preparation of viral antigens. It is important to stress that the viral antigens found in tumors are not host specific, i.e., the same antigens are found in tumor cells of all species. Thus, these CF antigen studies appear to provide a potentially highly important tool for etiologic studies, both for finding viral antigens in tumors and for seroepidemiologic studies with "tumor-specific" viral antigens.

In conclusion, I should like to apologize for having presented what may seem a collection of truisms and hypothetical speculations; it may seem that defining etiologic criteria for human cancer viruses in the absence of first-rate candidates is premature. However, to some extent these are very real questions; viruses are being isolated from tumors, and it seems advantageous to have some concept of the etiologic problem and some framework of how to deal with it lest we make too much of our findings, or, perhaps worse, make too little of them and pass off significant findings as being obviously chance associations.

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