ONCOGENIC VIRUSES

(with particular reference to Mouse Leukaemia)

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by

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IT HAS LONG been suspected that malignant tumours and allied disease, such as leukaemia and the various forms of lymphomas, are caused by transmissible viruses.† However, theories advancing viral origin of tumours were difficult to sustain. There were several reasons which did not appear to favour a concept of infectious origin of cancer; among such reasons were the following observations: (*a*) it is common knowledge that tumours, which are treated and dissected daily by physicians in many hospitals without any particular precaution, are not transmissible from one person to another by contact infection; (*b*) malignant tumours can be induced by ionizing radiation, carcinogenic chemicals, hormones, or a variety of physical factors, such as prolonged local exposure to heat, chronic irritation, etc.; (*c*) tumours and leukaemia have been observed to occur more frequently in certain families than in the general population (Table I); this familial incidence of tumours has been observed not only in several animal species, such as mice or cattle, but also in humans.

These observations appeared to suggest that a variety of factors, possibly non-specific or of genetic origin, but unrelated to viruses, may be responsible for the development of cancer and allied diseases, including leukaemia, in animals as well as in man. The concept of " somatic mutation " became popular as one of the possible explanations of the aetiology of malignant tumours.

On the other hand experimental data became gradually available, suggesting that at least certain tumours in chickens, frogs, rabbits, mice and rats could be transmitted from one host to another by filtrates. These observations were in striking contrast to the genetic theories of the origin of cancer, and suggested instead that at least certain malignant tumours are caused by filterable viruses.

It should be emphasized at this point that our means of determining the nature of an obscure disease are limited. An attempt is usually made to

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† For a more detailed discussion of this subject, the interested reader is referred to a recent monograph of the author on *Oncogenic Viruses* published in 1961 by Pergamon Press, in Oxford.

transmit the disease from one host to another by experimental inoculation. It has long been recognized that if a disease can be transmitted by inoculation of a filtered extract prepared from diseased tissues, it can be usually assumed that such a disease is caused by a submicroscopic, filterable and transmissible virus.

Thus, on the one hand speculation and theories on the origin of cancer appeared to favour a non-viral origin. On the other hand, experimental data gradually became available suggesting that at least certain tumours in animals are caused by filterable and transmissible viruses.

TABLE I

SOME OF THE COMMON OBSERVATIONS ON CANCER AND ALLIED DISEASES, WHICH INFLUENCED THEORIES ON ITS NON-VIRAL AETIOLOGY

1. Not transmissible in conventional manner (such as contact exposure).
2. More frequent in certain families, than in average population.
3. Can be induced by a variety of non-specific factors, such as:
   - (*a*) Ionizing radiation
   - (*b*) Carcinogenic chemicals
   - (*c*) Hormones
   - (*d*) Chronic irritation.

Experimental transmission of tumours by filtrates

In 1908, Ellerman and Bang reported that leukaemia in chickens could be transmitted by filtrates. This observation made over half a century ago established for the first time the fact that leukaemia in chickens is of viral origin. Three years later Peyton Rous (1911) demonstrated that chicken sarcoma could also be transmitted by filtrates.

Two decades elapsed during which not much additional progress has been made in this field. In 1932 and 1933 Richard Shope demonstrated that fibroma and papilloma in rabbits could be transmitted by filtrates. Shortly thereafter Baldwin Lucké reported (1934, 1938) that a carcinoma of the kidney in the frog could be also passed by cell-free extracts. At about the same time, John J. Bittner (1936) reported that mouse mammary carcinoma is caused by a transmissible and filterable agent, transmitted from one generation to another in the milk of nursing females.

These were the initial observations demonstrating that a variety of tumours in chickens and mice are caused by filterable viruses.

In the meantime it has also been recognized that a variety of papillomas, warts and related growths in humans (Ciuffo, 1907; Wile and Kingery, 1919), horses (Cook and Olson, 1951), cattle (Magalhães, 1920; Creech, 1929), dogs (Findlay, 1930; DeMonbreun and Goodpasture, 1932) and other species, could be transmitted by filtrates, and are therefore caused by transmissible viruses.

Transmission of mouse leukaemia by filtrates

Since leukaemia in chickens has long been known to be caused by a virus, it was only logical to suspect that the same disease in other species also, including mice, rats and possibly humans, may be caused by similar transmissible agents. Repeated attempts, however, to transmit leukaemia in mice and rats by filtrates failed prior to 1951.

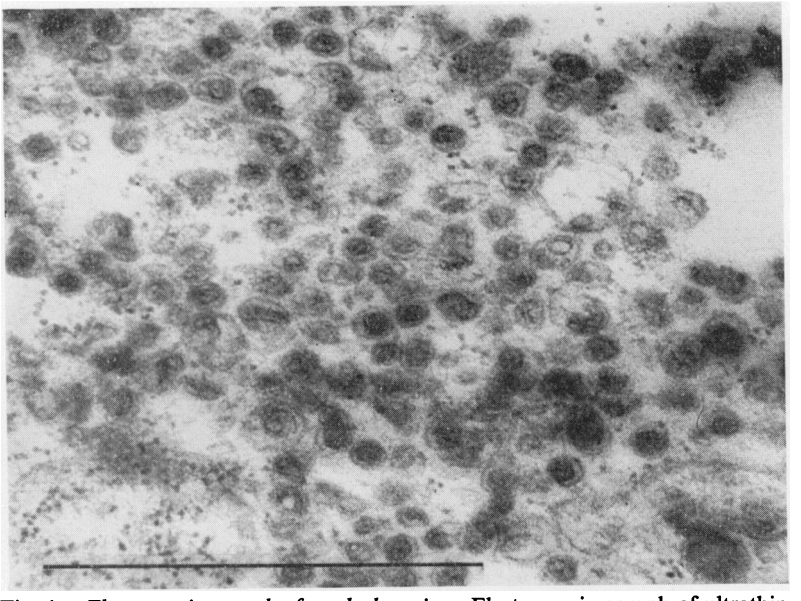

Fig. 1. *Electron micrograph of rat leukaemia.* Electron micrograph of ultrathin section of a thymic lymphoma from rat leukaemia, induced by the passage A mouse leukaemia virus (Gross). On this electron micrograph only part of the cytoplasm of the cell is seen, showing a large number of spherical virus particles. Some of the particles have an electron-dense nucleoid centrally or excentrally located, surrounded by one or two membranes; other particles have an electron-lucent centre surrounded by two or three membranes. Average diameter of particles approximately 100 mμ. (Magnification 60,000 ×.) Electron micrograph from a study by Leon Dmochowski, Ludwik Gross, and Frank Padgett from the M. D. Anderson Hospital and Tumor Institute, Houston, Texas, and Cancer Research Unit, Veterans Administration Hospital, Bronx, N.Y.

A turning point in the study of experimental mouse leukaemia was marked in 1951, when cell-free transmission of lymphatic leukaemia in mice succeeded in our laboratory; filtrates prepared from leukaemic mouse tissues induced leukaemia following inoculation into newborn mice of a susceptible, but relatively free from spontaneous leukaemia, strain of mice (Gross, 1951).

Initial attempts to reproduce this experiment, and to transmit spontaneous mouse leukaemia by filtrates, were fraught with difficulties

(Gross, 1961). The preparation of active leukaemogenic filtrates from organs of leukaemic mice was not always readily accomplished; most of the leukaemic mouse donors yielded filtrates of low infectivity, or filtrates which were not infective at all. It was therefore of considerable practical importance that a potent virus strain could be isolated from a leukaemic Ak mouse (Gross, 1957). This virus has been maintained by serial cell-free passage through newborn C3H mice; its potency gradually increased, and became stabilized. The leukaemic " passage " virus now induces leukaemia in practically 100 per cent. of animals following inoculation into newborn, or suckling, three to seven day old, mice of several inbred strains. This virus is also pathogenic for young adult mice; however, when inoculated into adult animals it induces disease after a relatively longer latency; moreover, the incidence of disease induced under such conditions is lower than that resulting from inoculation of newborn or suckling animals.

The mouse leukaemia virus is also pathogenic for newborn rats (Gross, 1961); it induces leukaemia in most of the inoculated animals; the virus can be recovered from the leukaemic rats and passed serially, by filtrates, from rats to rats. The disease induced in either mice or rats develops after a latency varying from six weeks to several months, usually after about two to three months.

Various forms of leukaemia can be induced with the leukaemic virus in mice and rats. In certain strains of mice, lymphoid leukaemia results in practically all inoculated animals; in other strains, however, up to 30 per cent. of the inoculated animals develop the myeloid form (Gross, 1963). Stem-cell leukaemia is quite frequent; lymphosarcomas or reticulum-cell sarcomas also develop in some of the inoculated animals. In the rat, either lymphatic or stem-cell leukaemia usually develops following inoculation of the virus; in some instances, however, the myeloid form is induced (Gross, 1963).

The curious role of the thymus

Mice of the C3H strain, an inbred line which we have been using in most of our experiments, developed usually lymphoid leukaemia as a result of inoculation of the leukaemic virus. When the thymus was removed in these mice by a surgical procedure, the development of leukaemia was considerably delayed; some of the thymectomized animals remained in good health even though they had received the virus. A few of the thymectomized mice developed later in life myeloid leukaemia (Gross, 1959, 1960). When filtrates prepared from myeloid leukaemia were inoculated into newborn mice, lymphatic leukaemia developed in most of the inoculated animals (Gross, 1960, 1962). Thus it is quite apparent that the leukaemic virus can induce either lymphatic or myelogenous leukaemia.

The removal of the thymus did not, therefore, entirely protect such mice from the leukaemogenic action of the virus; it offered, however, partial resistance to some animals, and changed the form of induced disease in others. It is possible that in mice of certain strains the presence of thymus is necessary for the leukaemogenic action of the virus, and early development of the disease. In the absence of thymus, the leukaemic virus may select other organs, such as spleen, liver, peripheral glands, or bone marrow, to initiate disease; a considerable delay, however, may occur in

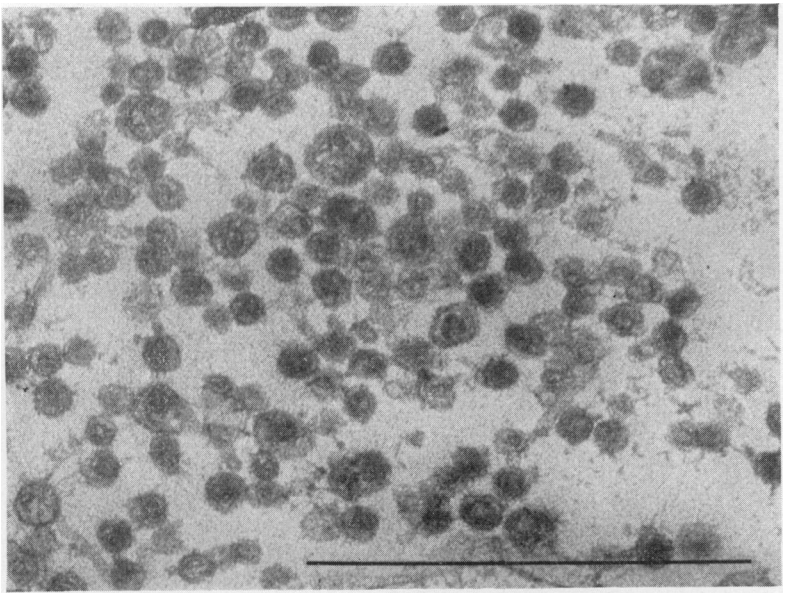

Fig. 2. *Electron micrograph of human leukaemia.* Electron micrograph of ultrathin section from a lymph node of human leukaemia. Only a small segment of cytoplasm of a cell is seen, showing a large number of spherical particles very similar in size and morphology to those described in Figure 1. From a study by L. Dmochowski, C. D. Howe, C. E. Grey and C. C. Shullenberger, from the M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

such instances; many thymectomized animals may live out their usual life span, and may die from other causes, before conditions favouring the development of leukaemia may occur.

The influence of thymectomy on susceptibility to the leukaemic virus was also studied in rats (Gross, 1963). In this series of experiments newborn rats of the Sprague-Dawley strain were inoculated with the passage A leukaemic virus shortly after birth; thymectomy was performed on these animals when they were approximately 10 days old. There was a marked

delay in the development of leukaemia in the thymectomized rats as compared with the controls. The incidence of myeloid form of leukaemia in the thymectomized rats was about twice as high as that in the controls. Furthermore, one rat in the thymectomized group developed erythromyeloid leukaemia. The influence of thymectomy on the susceptibility of rats to the leukaemogenic action of passage A virus was therefore essentially similar to that previously observed in mice.

Presence of a latent leukaemic virus in transplanted mouse tumours

One of the most interesting observations made during the past several years was the induction of leukaemia in mice with filtrates from transplanted mouse carcinomas or sarcomas. These significant experiments were first carried out by Graffi and his associates (1956, 1958) and were later repeated, and extended, by other investigators (Moloney, 1960). It appears that some of the transplanted mouse tumours used for these experiments contained a latent leukaemogenic agent only as an incidental companion. In the course of many successive cell transplantations, these tumours might have picked up a leukaemogenic agent from some of the mice employed for tumour grafts. Such a leukaemogenic agent could have remained latent, even though carried along with the tumour grafts from one transplantation to another. Under favourable conditions, when cell-free extracts prepared from such tumours were inoculated into newborn mice of a susceptible strain, the leukaemogenic agent, hitherto latent, could become pathogenic and cause the development of leukaemia in some of the inoculated animals.

Radiation-induced leukaemia

The leukaemic virus, present in a latent form in normal, apparently healthy mice, could be also activated by total-body X-ray irradiation. This was demonstrated in a series of experiments carried out in our laboratory, in which normal healthy mice of families which usually remain free from leukaemia were irradiated; about 60 per cent. of the irradiated mice developed leukaemia. Filtrates prepared from such leukaemic animals reproduced leukaemia, following inoculation into newborn mice (Gross, 1958). In this experiment, therefore, X-ray irradiation activated a previously latent virus. Once activated, the virus could then be passed serially through successive cell-free passages in mice (Gross, 1959).

Leukaemic viruses presumably exist in many normal mice, without causing disease. They are transmitted naturally from one generation to another directly through the embryos (Gross, 1951, 1955). Under certain conditions the leukaemic virus may also be present in the milk of leukaemic female mice, and thus infect their offspring (Law and Moloney, 1961; Gross, 1962).

The parotid tumour (polyoma) virus

In the initial experiments dealing with the isolation of the leukaemic virus from leukaemic mouse tissues, the unexpected observation was made in our laboratory that among the newborn mice inoculated with leukaemic filtrates, a few developed, instead of leukaemia, carcinomatous tumours of the salivary (parotid) glands (Gross, 1953). It was determined in these early studies in 1953 that the leukaemic extracts contained two distinct viruses: one was the leukaemic virus, and the other was a different oncogenic virus capable of inducing tumours of the salivary glands, and also related neoplasms, such as subcutaneous sarcomas (Gross, 1953). This second virus, designated in our earlier studies as the " parotid tumour virus ", was later grown in tissue culture by Drs. S. E. Stewart, B. E. Eddy and their co-workers at the National Institute of Health (Stewart *et al.*, 1958). The tissue-culture-grown parotid tumour virus, also known as the " polyoma virus " (Eddy *et al.*, 1958), was found to be very potent and capable of inducing a variety of tumours in mice (Stewart *et al.*, 1958), hamsters (Eddy *et. al.*, 1958) and rats (Eddy *et al.*, 1959).

The parotid tumour (polyoma) virus is a spherical particle, approximately 33 to 40 mμ in diameter; on electron microscopic examination of ultra-thin sections, the polyoma virus particles were found in the nuclei of the infected cells. On the other hand, the leukaemic virus particles are much larger, averaging about 100 mμ in diameter, have a characteristic single or double membrane, and can be found either in the cytoplasm or in the intercellular spaces of leukaemic cells.

The polyoma virus is rather resistant to heat; a temperature exceeding 70° C. is required for its inactivation, whereas the mouse leukaemia virus is inactivated by heating to 50° C. for 30 minutes. Thus, the polyoma virus differs from the leukaemic virus, not only in its pathogenic potential, but also in its size, morphology, location in the infected cell, resistance to heat, etc.

It should be stressed that the polyoma virus remains usually latent and harmless under natural conditions of life. Mice infected naturally remain as a rule in good health, even though they carry and spread this virus. Spontaneous development of tumours, caused by this virus, is exceedingly rare; only very few cases of tumours developing spontaneously in mice naturally infected with the polyoma virus have been reported. This virus is widely prevalent in mice of different strains, and also in wild mice apparently unrelated to any laboratory strain. The same virus, however, when isolated from mouse tissues and grown in tissue culture, acquires a formidable pathogenic potential; harvested from tissue culture tubes and inoculated into newborn mice, rats, or hamsters, it may induce in most of the inoculated animals a variety of progressively growing neoplasms.

The S.V.40 virus and its cancer-inducing potential

Viruses are commonly carried by many animal species, including monkeys, and appear as contaminants in cell cultures of their tissues. It is not surprising, therefore, that normal healthy kidney cells from monkeys contain a considerable number of latent viruses.

Hull and his co-workers (1957) studied viruses observed in normal monkey kidney cell cultures and called such latent viruses " simian viruses" (S.V.). Some 40 of such viruses were recorded. Sweet and Hilleman (1960) described a latent virus recovered from normal monkey kidney cells. This virus designated by the symbol S.V.40 was of particular interest; it could be regularly recovered from *rhesus* and *cynomolgus* monkey kidneys, causing no changes in kidney cell cultures from such monkeys; the same virus, however, caused marked cytopathic changes in cell cultures of the " green monkey " (*cercopithecus aethiops*), a species obtained from Equatorial East Africa. Because of the prominent cytoplasmic vacuolation seen in infected green monkey cell cultures, the S.V.40 virus was also called the " vacuolating virus " by Sweet and Hilleman (1960).

The S.V.40 virus was therefore present in many of the kidney cell cultures prepared from *rhesus* and *cynomolgus* monkeys, routinely employed for the preparation of polio vaccines. It was not surprising, therefore, that the S.V.40 virus was found in the early batches of all three types of the live attenuated Sabin poliomyelitis vaccine. Since the S.V.40 virus is relatively resistant to formaldehyde, some of the early lots of the inactivated (by formaldehyde) poliomyelitis vaccine of Salk were also found to be contaminated by the S.V.40 virus. Unexpectedly, Eddy (1961, 1962), Girardi (1962) and their associates reported that the S.V.40 virus is capable of inducing a high incidence of malignant tumours following inoculation into newborn hamsters. This observation caused considerable consternation since it was realized that a certain number of infants that had been inoculated with the early batches of both the Sabin vaccine and the Salk polio vaccine also received the S.V.40 virus.

Fortunately, there is no definite evidence at this time to suggest that the S.V.40 virus could induce tumours in humans. It is hoped that this virus will remain latent in humans as it is latent in its natural host, the *rhesus* and *cynomolgus* monkey. In any event, considerable precautions are now employed in the preparation of the Sabin and Salk types of poliomyelitis vaccine to assure that none of them contains the S.V.40 virus.

It is quite apparent, nevertheless, that utmost caution is required when live tissue-culture-grown viruses are employed as vaccines, and when such vaccines are to be inoculated into newborn infants. Tissue culture cells contain latent viruses; no tissue culture cell system is sterile. Some of the

latent viruses carried in " normal " cells employed for tissue cultures could eventually prove to be oncogenic. The danger would appear much less acute if such vaccines were inoculated into children beyond their first few years of age. Newborn hosts are particularly susceptible to the carcinogenic action of oncogenic viruses. The susceptibility to such viruses decreases rapidly with advancing age. Even in hamsters, relatively large doses of the S.V.40 virus had to be inoculated, preferably by subcutaneous route, into newborn or suckling animals, in order to induce tumours. When hamsters more than one month old were inoculated, no tumours resulted (Girardi *et al.*, 1963).

Human adenovirus type 12 and its cancer-inducing potential for hamsters

There exists some 28 different types of human adenoviruses; they are related and designated by type numbers. These viruses may cause in humans uneventful and self-limited diseases such as upper respiratory infections, or conjunctivitis of the eye. The possible pathogenic potency of many of these viruses, however, still remains obscure. It is assumed that at least some of them may remain latent in man (Rowe *et al.*, 1957).

TABLE II

SOME OF THE MORE IMPORTANT ONCOGENIC VIRUSES

1908	Chicken leukaemia	Ellermann and Bang
1911	Chicken sarcoma	Rous
1932	Rabbit fibroma	Shope
1933	Rabbit papilloma	Shope
1934	Frog kidney carcinoma	Lucké
1936	Mouse mammary carcinoma	Bittner
1951	Mouse leukaemia	Gross
1953–57	Mouse parotid tumour (polyoma) ..	Gross-Stewart-Eddy
1960–61	Vacuolating simian virus 40 (oncogenic for hamsters)	Eddy and co-workers
1962	Human adenovirus Type 12 (oncogenic for hamsters)	Trentin and co-workers

Surprisingly, human adenovirus type 12 was found by Trentin *et al.* (1962) to be carcinogenic for hamsters. This virus induced a high incidence of malignant tumours following inoculation into newborn hamsters.

Huebner and his associates (1962) confirmed this observation and found that adenovirus type 18 is also carcinogenic for newborn hamsters.

There is no evidence thus far to suggest that either adenovirus type 12 or 18 is responsible for the development of some of the tumours in humans. It is of considerable interest, nevertheless, that a human virus was found to be carcinogenic for animals.

Conclusions

To summarize, a variety of sarcomas, certain carcinomas, as well as different forms of leukaemia and lymphomas in chickens and mice were found to be caused by filterable and transmissible viruses. It appears

that very frequently such potentially oncogenic viruses are carried by many normal and perfectly healthy hosts. These latent viruses may behave like " perfect parasites ", be frugal and moderate in their requirements, and cause no apparent harm to their hosts. The latent oncogenic viruses may carry, however, a formidable pathogenic potential. When triggered into action, they may change from harmless parasites into pathogenic agents; the activated viruses may prompt rapid multiplication of cells harbouring them, causing the development of leukaemia or other tumours, according to the type of oncogenic virus carried by the host (Table II).

The main feature distinguishing oncogenic viruses from other pathogenic viruses is the fact that they can cause neoplasms; in other respects, however, oncogenic viruses do not represent a class fundamentally different from other animal viruses. Most of them are submicroscopic particles, usually of spherical shape, and varying in diameter from 30 to 120 mμ. They can be visualized with the electron microscope; some of them, such as the virus of chicken sarcoma, mouse mammary carcinoma, or mouse leukaemia, can be found in the cytoplasm of infected cells, or in intercellular spaces; other oncogenic viruses, such as the parotid tumour (polyoma) virus, the S.V.40 virus, the adenoviruses, the rabbit papilloma and human wart viruses can be found in the nuclei of infected cells.

Oncogenic viruses can be grown in tissue culture. They are antigenic to a varying degree, and can be neutralized by specific immune-sera.

Oncogenic viruses can induce tumours following inoculation into susceptible hosts; newborn hosts are as a rule more susceptible than adult animals. Under the usual experimental conditions most of the oncogenic viruses induce a particular form of a tumour in a given species of host. Some oncogenic viruses can produce different forms of tumours in several species of hosts. In most instances, however, the oncogenic viruses remain latent under natural conditions of life. Certain viruses such as S.V.40 may be as a rule latent when carried in one species of hosts, but may cause tumours if transferred to another host species. It also appears that some viruses, such as adenovirus type 12 or 18, may cause a variety of transitory, inflammatory disorders in one species, but may be oncogenic in another species of hosts.

A working hypothesis

The development of tumours or leukaemia in several members of a family, possibly in several successive generations, may be interpreted by a working hypothesis explaining the induction of such tumours by latent oncogenic agents transmitted naturally in certain families from one generation to another.

On the basis of this working hypothesis, one could therefore regard the development of cancer or leukaemia as the result of an activation, fre-

quently merely accidental, of an oncogenic agent, hitherto masked, and carried by the host since birth. The activation of an oncogenic agent could be prompted by a number of varied, generally non-specific, factors. The inducing factors could be (*a*) external, such as ionizing radiation, or certain chemical cell poisons, or (*b*) internal, that is of metabolic or hormonal origin. Only some of the tumour-activating factors are known; most are still obscure.

Should the experimental observations obtained on mice be directly applicable to humans, it would follow that individuals suffering from malignant tumours or leukaemia represent only a small fraction of those actually carrying the seeds of either disease (Gross, 1954).

Recent observations dealing with the oncogenic potential of the S.V.40 virus and of adenovirus types 12 and 18 suggest that a virus which may be either completely latent, or able to induce only a minor disease in one species, may at the same time be capable of inducing malignant tumours in another species of hosts.

Since viruses carried in a latent form in either monkeys or humans may induce tumours in animals, it is possible to speculate that the reverse may be true also. There may exist viruses which are carried in a latent form in some animal species; the same viruses may be potentially carcinogenic for other host species including humans.

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