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S. E. polyoma virus: A provocative discovery

S.E. POLYOMA VIRUS

A PROVOCATIVE DISCOVERY

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Table of Contents

INTRODUCTION:

The history of cancer research has been one of interesting speculation, theorization, and renewed investigation. Yet the tumor problem still remains in a state where facts are not strong enough to kill fancy. Perhaps the most current view is that of a viral etiology of cancer. Viruses are loosely defined as minute (filtrable), replicable, and transmissible (infective) particles.[46]

Proponants of a viral etiology of cancer received their impetus from two sources. First, viruses have experimentally been shown to have actual tumor producing properties, and are now recignized as having some part in the generation of certain tumors.[9] Second, new techniques have made it possible for virologists to isolate many new viruses from man. Huebner reports of at least fifty new viruses of man, of many new viruses on the horizon, and of untyped agents by the hundreds accumulating faster than they can be characterized and classified.[45]

The tumor problem has been regarded as the last stronghold of metaphysics in medicine.[66] Indeed, it is tempting to anticipate carcinogenic activity in at least one of these newly discovered viruses.

In spite of the steadily mounting number of viral tumors of animals and the unprecedented isolation of human host viruses, the only established human viral tumor is the lowly wart.[2,28] Nevertheless, thoughtful consideration of a viral etiology of cancer is not unfounded. There is a new basis for optimism that diseases of viral origin will provide the principles useful in approaching human cancer. Virus tumors provide an inexhausti-

ble wealth of material for study in the fundamental aspects of viral disease as well as cancer. It is hoped that these observations will ultimately directly relate to the occurance of cancer in man. Although this relationship is still not clearly defined, it is of importance to realize that studies of animal tumors have resulted in new methods of research suitable for exploring and approaching cancer in man.

HISTORY OF VIRAL TUMORS:

The virus - tumor relationship cannot be understood without quickly looking into the past.

The first virus was discovered in 1892 by Iwanowski[47] and was confirmed in 1899 by Beijerinck.[11] Shortly thereafter, Ellman and Bang (1908) discovered the first tumor inducing virus as the causitive agent in chicken leukosis.[11] 1911 heralded the discovery by Rous of the chicken sarcoma and osteochondrosarcoma viruses.[65]

By 1928 the number of viral associated fowl sarcomas was observed to reach 18 and each was proported to produce only one type of tumor.[10]

Shope in 1932 reported a viral induced fibroma in the rabbit,[77] and just one year later reported a fascinating rabbit papilloma which eventually converted to carcinoma. The fascinating fact being the eventual disappearance of the virus in the papilloma - carcinoma sequence.[78]

A discovery standing in lonely eminence during this early period of understanding can be claimed by Bittner and his mammary tumor inducing virus (1936).[6A] This was the first known mammalian carcinoma caused by a virus.

The discovery of the "milk factor" culminated thirty years of study on mammary tumor in mice and was brought about by the intro-

duction and development of inbred strains of mice originated by E. C. Little in 1909.[56]

It is all the more to the credit of Bittner that he pointed out the equal importance of age, hormonal componant, and genetic background of the host, in the viral induction of tumors.[6]

POLYOMA VIRUS: DISCOVERY:

Research has progressed rapidly in the short fifty-two year span of experimentation relating virus and tumor. Presently, the S.E. polyoma virus (1957) has received considerable attention.

In itself, this virus has neither directly nor indirectly implicated a viral causation of human cancer. However the elaboration of this agent's activity has drawn upon the legacy of past experience while utilizing latest methods of research which are also suited for investigating the nature of cancer in man.

A review of the polyoma virus is worthwhile, not only for an exposure to the methods of investigation, but also because "Viruses are in the tumor problem to stay".[18]

The discovery of polyoma virus was a direct result of Sarah Stewart's attempt to verify the reports of another investigator who had induced leukemia in healthy mice with cell-free filtrates from leukemic mice. Ludwig Gross had accomplished this brilliant result by making cell-free extracts from the diseased organs of the leukemic susceptible AK mouse strain, and introducing them into new born mice of strains C3H and C57, both of which are highly resistant to the spontaneous development of leukemia. Within three months as many as 56% of the recipient mice had developed leukemia.[31,32] Although new born mice had been used before,[6] Gross was the first to utilize this innovation in the field of mouse leukemia and was the first to be rewarded.

Although Gross' results had been confirmed by Wooley,[91] Stewart was unable to reproduce them. For an unknown reason, her C3H mice remained resistant to the tissue extracts of leukemic AKR mice.[81] Acting on the assumption that the genetic constitution of the C3H strain might be affording some protection against a possible naturally occuring agent in the tissue extracts, a hybrid strain was developed. It was a cross between leukemic susceptible and resistant strains (C3H x AKR)f1. In the first experiments, AKR filtrates indeed produced leukemia in the hybrids. In addition it was noted that hybrid mice, receiving filtrates from spontaneous leukemic hybrids, developed either leukemia or solid tumors (parotid or adrenal).[81,82]

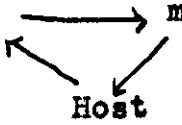
Why Stewart's C3H mice maintained their resistance to leukemic extracts remains a mystery. Wooley suggests that the development of leukemia and other tumors seems to depend on the preparation and the genetics of the recipient host.[91] Even Wooley deviated from Gross on occasion when it was noted that leukemia did not occur in animals in which sarcoma or parotid tumors had developed. It was further suggested that the method of extract administration might be a significant variable.[50]

Solid tumor production after introduction of leukemic extracts was not unique. Gross had previously reported the appearance of parotid and myxosarcomatous tumors as incidental findings,[36] which he later elaborated upon.[33,37,38].

It remained for the newly formed team of Stewart and Eddy to serially pass their virus in tissue cultures of monkey kidney and Swiss mouse embryo, to realize the full potency of the agent. Growth in tissue cultures rendered the polyoma virus worthy of its name. It has produced a total of twenty-three primary

neoplasms and has crossed species barriers in doing so.[83] Neoplasms have been produced in mice, rats, hamsters, and rabbits.

In developing a potent virus, agent, tissue culture and host were intimately related in a manner which can be schematically represented as follows:



The inquiring mind asks the nature of the agent, tissue culture, and host. What is their individual contribution to the pathogenic effect and how are they related?

THE AGENT: POLYOMA VIRUS

Isolating and characterizing the virus has revealed that it is fairly stable in retaining its infectivity and ability to grow in tissue culture after a variety of "insults".[84] S.E. virus was stable after storage from one hundred sixty-nine to four hundred four days at temperatures ranging from -70° C to 4° C. Wheras 80° C destroyed tumor producing properties, exposure at 60° C for one hour, or 70° C for thirty minutes, merely impaired this property. The virus can withstand lypholization.

Additional studies[7] showed that polyoma virus was relatively resistant to ultra-violet light, 2% phenol, 50% ethyl alcohol, ether, glycerol, and trypsin. However it was sensitive to 100% ethyl alcohol, and alcohol iodine.

The size of the virus was roughly determined with gradocol membranes and was found to be 43-73 μ.[21]

Electron microscopy revealed that polyoma has a characteristic size and shape. It is a particle of 40 -45 μ shaped as a flattened oblate spheroid 59 μ in major diameter and 24 μ in minor diameter.[49] These measurements are within the range re-

ported by Stewart and Eddy[21] (73 ± -43 ±) and by Gross of the leukemic virus (30 ± -70 ±).[34]

Other properties of polyoma virus have been demonstrated through serological testing. It agglutinates guinea pig, hamster, and human "O" erythrocytes at refrigerated temperatures.[19,44] Hemaglutination has been used as an assay for polyoma, however this is the least sensitive of the assays. Those to be preferred are induction of tumor in hamsters and cytopathogenicity in mouse embryo cells.[20]

Prior treatment of erythrocytes with vibrio comma renders the red cell non agglutinable with polyoma virus.[43] A similar phenomenon was noted when guinea pig erythrocytes were pre-treated with both myxovirus and influenza virus.[43]

TISSUE CULTURES:

Growth in tissue culture was a necessary step in developing the tumor producing capacity of the polyoma virus.

A proven non-infective extract of mouse parotid tumor, became infective in some mice after being cultured on Rhesus monkey kidney tissue in which only minimal changes had occurred.[22,84]

It was later found that minced Swiss mouse tissue proved to be a superior culture medium.[83] The degeneration of these virally infected cells resulted in plaque formation, which become an assay for the virus;[14,90] for the amount of plaque formation and virus are directly related, as is the amount of virus and neutralizing anti polyoma rabbit serum required to prevent plaque formation.[90]

In addition, multiple passages across species barriers result in increased plaque production, thus indicating a correlation between infectivity and cytopathogenic effect seen

in tissue culture.[21]

Another desirable quality of mouse embryo tissue culture, is the yield of pure lines of virus which is a consequence of the slow release of polyoma virus from tissue culture cells.[69]

A cytopathogenic effect produced by polyoma virus has also been described in cultures derived from a murine malignant lymphoma.[64] Of interest is the rapid production of the cytopathogenic effect which makes the system suitable for titration and growth studies of this agent. Since the cell strain grows in a serum free medium, it is possible to study infection during growth of the cell population in the absence of serum antibody and serum viral inhibitors.

Tissue cultures have proven to be an invaluable aid in the study of polyoma virus. The reason for increased infectivity is not known. It can only be theorized that tissue cultures serve as a means of removing the virus from the effects of neutralizing antibodies and may also serve as a means of providing cells wherein the virus could replicate itself.[85,71]

HOST

Host characteristics are critical in experimentation relating to virally induced tumors. The importance of age and species has already been noted in the works of Bittner, Gross, and Stewart.

Gross experimented with AK mice inbred for twenty years.[35] This strain developed minimal spontaneous parotid tumors but had a spontaneous leukemic incidence of 60%.[46] In later experiments Gross used mice of strain C58, 90% of which develope spontaneous leukemia.[46,59] Leukemic resistant strains were C57 and C3H. The development of spontaneous leukemia in the resistant

strains has been noted by some observers to be absent[46] and by others to be minimal (o.5%).[31]

Stewart and Eddy required a hybrid strain (C3Hf X AKR) to achieve their initial results.[22,23] The reported incidence of spontaneous leukemia in strain C3Hf is very low.[53] In their later experimentation with mice, Stewart and Eddy used inbred Swiss mice as did other investigators.[69]

The genetic liability of specific mouse strains to develope cancer has become empirically obvious. For this reason investigators have developed strains of mice to suit the conditions of their experiments. This practice has cast a shadow of impurity on viral induced tumors and leukemia.

Huxley points out that there is species variation in the incidence of spontaneous tumors.[46] McDowell[58] and Strong[87] emphasize that the existance of genes in mice determine their cancer proness to many types of tumors. Inbreading has built up several lines of high genetic impurity and has provided high biological magnification.[46,57]

It is thus concluded by these critics that all types of mouse cancer investigated by adequate methods have some genetic basis. That this conclusion is true cannot be denied. In fact it is readily admitted by most investigators in the field. Stewart is cognizant of the fact that the "leukemic incidence inbred mice is dependent on the genetic constitution of the strain..."[81]

The genetic constitution of a strain determines proness to spontaneously developed leukemia or tumors of the mammary gland, testicle, lymphoid tissue, pituitary gland or uterus.[46]

SPONTANEOUS

TUMOR TYPE

Mouse Strain	Mammary	Testicular	Lymphoid	Pituitary	Uterine
A	+++	+++	—	—	+++
C4H	+++	—	++	—	+++
CBA	++	—	+++	—	+++
C5 7BL	—	—	—	+++	+
JK	—	++	+	—	?
PM	—	—	++	±	+
H5	++	—	++	—	+

If Huxley's further view is correct that resistance is greatly reduced in genetically closely related members of long inbred strains, then the experimental results in the field must be weighed accordingly. If Huxley is correct, an imbred strain of leukemic susceptible as well as leukemic resistant animals are both susceptible to assaults by leukemic virus merely by virtue of inbreeding.

It does not seem to follow that inbred strains genetically resistant to the spontaneous development of leukemia will be susceptible to tumorogenic and leukemogenic assaults.

The S.E. polyoma virus has produced multiple tumors in several animal species,[70] not all of which were inbred.

Neoplasms of the lung, liver, kidney, heart, serosal tissue and subcutaneous tissues has occurred in golden hamsters after inoculation with cell-free filtrates of cultured polyoma virus.[25]

During the first twenty-four days of life, solid angiomatous tumors were induced in the Syrian hamster.[86]

28% of the experimental group of Sprague - Dawley rats developed renal cell sarcoma in contrast to less than 1% of the

control group.[23]

New born rabbits of a mongrel breed were the first of the non-rodents on which the effects of polyoma were tested. They reacted by developing multiple benign subcutaneous tumors that later regressed. 59% of the rabbits developed tumors from which the organism was isolated and was still infective to hamsters.[24]

The rabbit has a historical resistance against infection. Such was the case with the Shope fibroma reported in 1932. This neoplasm also later regressed.[41]

As yet Doctors Stewart and Eddy have not been able to infect monkeys with their virus, but an effort to do so is underway at Roswell Park Institute where a baby monkey was found to be harboring polyoma virus.[89]

RESPONSE OF THE HOST:

A great variety of malignancy has been manifested in the varied animal species just mentioned. The development of benign, rather than malignant growths, may be a reflection of species differences in response of the host to S.E. polyoma virus, (rabbit).

In the mouse, parotid gland tumors were most frequently seen, (96%),[86] but a variety of other neoplasms was also present. As many as eight histologically different tumors have been induced in one mouse.[24] Multiple sarcomas and angiomatous lesions developed in the heart, liver, and kidneys of the hamster; and sarcomas or angiomatous lesions developed in the kidneys or subcutaneous tissue of the rat.

Humoral antibodies against the S.E. polyoma virus have

been demonstrated in rabbits (after nodular regression), mice, and hamsters. This host defense may modify the response of polyoma virus, and thus influence the tumor type produced.

The in vivo effects of polyoma were aborted in hamsters and newborn mice by the administration of rabbit antiserum one hour before the introduction of polyoma. However protection was not apparent when antiserum followed polyoma virus by one hour.[86] Rabbit antiserum also inhibits plaque production in tissue cultures.[21]

All infected Swiss mice were found to have S.E. polyoma antibody.[70] The mouse antibody system is capable of responding early in life.[70,68] It is a sensitive and reliable system in that antibodies have been found prior to other evidence of tumor,[70] and have enabled investigators to recognize that an animal can come into contact with polyoma, yet not suffer any apparent pathology.

Rowe found that polyoma virus had an epidemiological pattern of infection and that antibodies were distributed by mouse colony and not mouse strain.[68] The virus was spread from mother to litter or from litter to mother; from one generation to the next or from animal to animal of the same generation. The mode of natural infective spread was as might be expected, through urine, feces, saliva, transplacentally, and possibly through sperm.[70] Neutralizing antibodies were found by Stewart in mice with tumors, control mice housed in the same laboratory, personnel exposed to mice, and in uninoculated mice within the virus environment.[85]

Because of the high incidence of infectivity of polyoma

among mouse colonies, it has been suggested that control animals be free of polyoma antibody. Only then can the true incidence of spontaneous tumor be ascertained.[68]

It is generally agreed that host defenses against cancer probably exist to a significant degree. However a specific antigen indicative of cancer has thus far eluded the investigator of human cancer.[54,55]

It should not be thought that polyoma neutralizing or hemagglutination antibodies represent a serological response to cancer. These are merely responses of a host infected with polyoma virus. There is often a lack of correlation of polyoma antibody with the occurrance of spontaneous leukemia in AK mice. This suggests that polyoma has little or no etiological relationship to spontaneous AK leukemia.[68] It was further noted that polyoma antibody was found in 100% of Gross' AK three month old mice, while no polyoma antibody was found in a leukemic AK colony of another investigator.[67,68]

In discussing the relationship of virus to host, the question of host age has already been noted. Although the reason why young mice are susceptible to Gross' leukemic factor and the S.E. polyoma factor remains to be answered, several views have been forwarded on the subject.

Could susceptibility lie in the newborn host's inability to form antibodies?

Sachs found an inverse relationship between antibody production and tumor induction in Swiss mice. No tumors were evident in mice challenged at the age of two weeks.[70]

days	tumor response to polyoma in Swiss mice
2	61/68
7	some tumors
14	no tumors

This pattern was extended in utero. Early death and increased cancer incidence occurred in Swiss mice inoculated in fetal life.[80]

An interesting question has been raised as to whether metabolic activities conducted in the comparative absence of certain enzymes are condition enough for the multiplication of certain viruses. As the animal ages, a full complement of enzymes is achieved and the animal's cellular metabolism now renders it resistant to viral multiplication.[54]

The synthesis of new viruses are mediated by enzyme systems of the host cells. It is thus not impossible that the availability or non-availability of enzyme systems might determine the existence of a resistant or susceptible strain. Immature rat brain is deficient in at least three enzymes, succinic dehydrogenase, cytochrome oxidase, and adenosine triphosphate.[54] Only future investigation will reveal deficiencies in other tissues.

Interestingly enough, as if flying in the face of reason, Friend has proved that newborn mice are not an essential condition for the viral induction of leukemia. Leukemia has been produced in all ages of mice and becomes apparent two to three weeks after inovulation.[27] In addition a formalinized

vaccine has conferred substantial protection against the induction of leukemia.[27]

MULTIPLE TUMORS:

A total of 23 primary tumors have been attributed to polyoma virus.[83]

Pleomorphic tumors of mucous glands:

- Parotid glands
- Submaxillary glands
- Sublingual glands
- Tracheal glands
- Harderian glands

Epithelial thymomas
Mammary adenocarcinomas in female
Mammary adenocarcinomas in male
Sebat-gland adenocarcinomas

Sarcomas:
- Renal
- Bone
- Other locations

Epidermoid carcinomas:
- Hair follicles, skin
- Mandible
- Stomach

Hamangioendotheliomas, subcutaneous
Liver hemangioma
Adrenal medullary tumors
Primary lung tumors
Papillary pleural lesion
Papillary lesion of epicardium
Thyroid-gland lesion
Kidney convoluted tubule lesion

There has been some speculation concerning the cause for the multiplicity of tumors seen in animals in whom cell-free extracts have been introduced.

Initially there was considerable discussion relating to the number of viruses present in each extract. Such questions were real and pertinent as far back as Gross' initial experimentation. He believed three distinct viruses were involved and that "inter-

ference phenomena" prevented all from manifesting themselves in the same animal. Thus separate viruses were responsible for leukemia, parotid gland carcinoma, and subcutaneous fibromyxosarcoma.[40] In support of this view, Gross demonstrated two viruses of different pore size by the use of gradocol membranes.[39]

The difference between the leukemic and parotid virus was "substantiated" by demonstrating that leukemic virus was ether susceptible and parotid virus ether resistant.[30]

These agents showed further variation in that only parotid virus was recovered from tissue culture.[30]

Although Stewart worked with leukemogenic extracts in the discovery of polyoma virus, the two organisms do not seem to be related. However, parotid tumor and polyoma virus bear some relationship in their mutual resistance to ether.[68]

Eddy recognized that an unequivocal answer could not be given concerning the number of etiological agents involved in the resultant multiple tumors. Yet indications pointed to a single agent.[20] Virus recovered from tissue culture fluid and infected tumor tissue had identical properties.[20] In addition gradocol membrane filtrates,[85] and election microscopic examination of various polyoma infected organs reveal a uniformity of viral size which is consistant with a single virus.[49] However, morphological similarity is not an absolute indication of identity.

If one virus is indicated, how then are such varied tumors explained? Perhaps the answer lies in the method of multiple passages between varied animal species.

When the hemorrhagic Rous sarcoma of chickens and ducklings was adapted to older ducks, turkeys and guinea fowl, a multitude

of tumors occurred. They included hemorrhagic disease, myxosarcoma, spindle cell sarcoma, lymphoid tumors, leukemias, angiomas, and endotheliomas.[15,16,17]

Thus the observations of Stewart and Eddy are another example of what happens after adaption of the virus to previously resistant species.

An example of this method of multiple passages as utilized by Stewart and Eddy is as follows:[20]

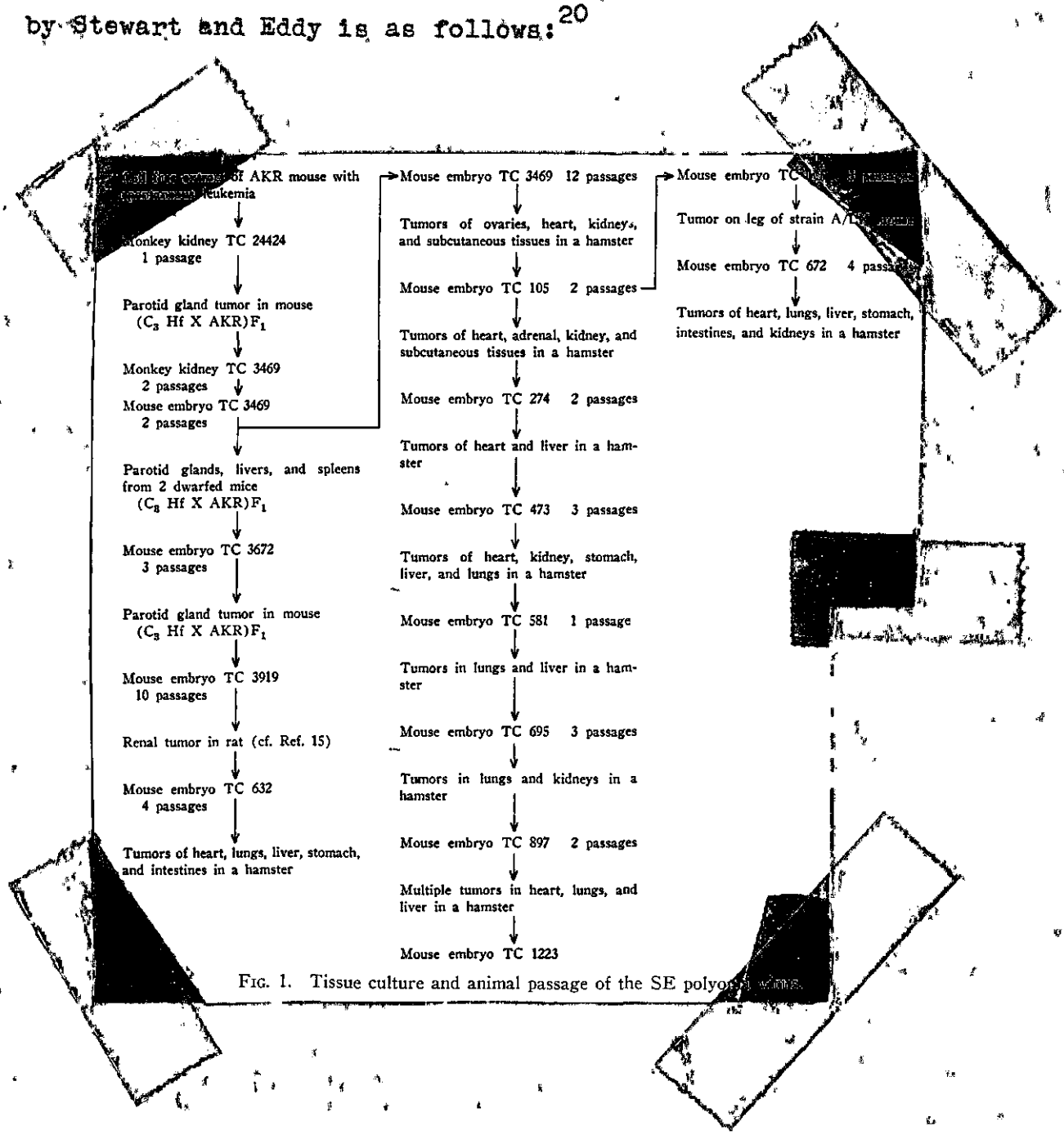


FIG. 1. Tissue culture and animal passage of the SE polyoma virus.

It should be remembered that the Rous sarcoma was not grown on tissue culture and that this latter procedure may be very important in the potency of polyoma.

A polyoma hemagglutination inhibitor, of an unknown nature, was found to increase hemagglutination titers by eight to thirty-two fold when dissociated by heat.[43] Furthermore, macromolecules present in tissue and tumor extracts were found inhibitory to polyoma virus[70] in vivo. The removal of these molecules by filtration enhanced the infectivity of the agent. Hence it does not seem unreasonable that there is some validity in the view that absorption of inhibitory macromolecules from polyoma by tissue culture is a contributing factor in multi tumor production.[8,71,79]

High speed centrifugation is another method by which removal of polyoma inhibiting agent can be achieved.[30,84]

Leukemic extracts (AK) which were centrifuged at high speeds produced parotid and other tumors in recipient newborn AK mice, but no leukemias. The tumors were the type produced by Stewart and her colleagues.[30] This result is of interest, for one may ask whether this tumor producing virus is in essence a leukemic virus with an inhibiting agent removed.

Is the parotid virus an unmasked leukemic virus? The removal of an inhibitor from the leukemic agent could account for the smaller sized parotid agent. However, this is not a simple matter. An inhibitor does not explain the difference between the two viruses in their susceptibility to ether, nor does it explain the differences between parotid and polyoma virus.

VIRUS AND HUMAN CANCER:

The ultimate forestated purpose in cancer research is its

applicability to man. The laboratory environs have yielded a considerable number of observations regarding the relations of viruses to laboratory animals. Among the specific techniques and methods used in conducting this experimentation, were electron microscopy, tissue cultures, high speed centrifugation, and inocculation into genetically acceptable animals.

If the ultimate purpose in cancer research is application of the results to man, it may be asked how these investigations relate to human disease.

Neutralization tests against polyoma virus of the animal protection method were carried out on human γ globulin, serum from hospital patients with malignancy, serum from patients in remission from neoplastic disease, and serum from laboratory personnel who had worked with polyoma virus. The mice were protected only with human γ globulin and the serum from a laboratory worker. The laboratory worker also had a hemagglutinin inhibition titer.[85]

The results of this experiment remain equivocal, for the effects of the globulin stabilizing agents have not as yet been tested, and reproduction of the results has thus far failed.[71] Therefore polyoma infectivity to humans remains undetermined.

Two investigators report the transmission of human leukemia into mice using cell-free filtrates and culture techniques.

Bergolitz, working with cell-free mitochondria fractions of varied human leukemic cancerous organs has produced leukemia in mice. The causative agent has been cultivated on allantoic chick embryo membranes and has been inactivated with heat and formalin. This agent is thought to be a virus one hundred to one hundred twenty-five μ in size.[3,4,5]

Shwartz reports the acceleration of leukemia in adult mice with leukemic human brain extracts.[74,75] The filtrates of human leukemic brain have also been passed serially in mice with no loss of leukemic stimulating activity.[73] It is of extraordinary interest that filtrates of leukemic organs have failed to yield the virus, with the exception of the brains of some mice.[73,75] This phenomenon has also been reported after the induction of leukemia in adult Swiss mice from donor leukemic mouse brain.[72,79]

The studies of both Bergolitz and Shwartz were well controlled and reliable. However, work in the field of human cancer transmission can be confused by overenthusiastic interpretation of experimental results. One investigator reports serial passages of cancerous human hypophysis in guinea pig adrenal which could be inhibited by serum from the original donor and which could be passed to plants.[26]

Electron microscopy has strongly implicated viral causation of some human cancer.

Dmochowski has observed viral particles within the lymph nodes of patients with acute lymphatic leukemia,[12] acute myaloid leukemia, and the bone marrow of myalogenous leukemia.[13] Ovoid "viral" objects have recently been reported within primary tumors and secondary metastasis of carcinoma of the colon.[62] These viral particles seem similar in some respects to previous demonstrations of viruses in animal tumors.

If indeed E/M has exposed true viruses in malignant human tissue, these may in fact be saprophytic. It is further recognized that a virus has never been isolated or cultivated from

a malignant human tumor. Yet in spite of these arguments, proponants of the viral causation of human cancer continue in pursuit of their thesis, citing the failure to isolate Shope papilloma virus from malignant tumor which it was known to induce.

A viral etiology of cancer implies transmissability of the agent and thus an infectious nature of cancer. Epidemiological studies of the natural spread of polyoma virus has been mentioned earlier in this paper.

Thoughts concerning the infectious transmission of cancer are reminiscent of a past scientific age. In the earlier days of the century, the so called parasitic theory of cancer was examined in great detail. Those were the days of belief in cancer houses, cancer regions, and cancer epidemics.[67] By an immensity of hard work, possibilities of amoebic, yeast, and bacterial causation of malignant growth were discarded.[67]

There has never been a proven case of human transmission of cancer through any natural medium. In this regard, Koch's postulates have never been fulfilled.

In spite of these historical considerations, Gross has submitted for consideration a theory of viral transmission of cancer. Transmission through contact or vectors is eliminated in the proposed vertical transmission theory.[40] Disease may be passed from host to offspring in much the same way as rickettsial infection is transmitted.[35]

The viral agent may be transmitted directly through germinal cells and remain in the host, resembling temperate bacteriophage in a lysogenic bacterial host. When activated, the virus may become a pathogen. Thus induction of leukemia by x-irradiation,

hormones, and chemicals could be explained by the vertical transmission theory, assuming that leukemia and allied neoplastic diseases are caused by viral agents.

Experimentation substantiates the possibility of a vertical transmission of leukemia in mice. Extracts of AK embryos were capable of inducing leukemia, thus they were infected in utero.[40] Furthermore, normal organs were leukemogenic, indicating latent virus.[33]

Unfortunately, Stewart made forty-three passages in tissue culture of four hundred Swiss mouse embryos, and was not able to find evidence of a tumor inducing agent. It was concluded that a latent tumor agent, if wide spread in a mouse colony, was not wide spread in utero.[83]

If the working hypothesis of vertical transmission is correct, increased familial incidence of cancer would be expected. Specific examples of familial occurrence of tumors and leukemia are cited by Gross.[40] However, there is considerable confusion whether increased family tumor incidence can stand the test of statistical analysis.

Although there is almost universal agreement that breast cancer is more prevalent among members of the same family,[48,61] a recent study[63] revealed that no statistical difference was apparent.

Not only does a viral etiology imply that the disease may be transmitted, but it also implies a form of control. As remote as it may seem, there has already been mention of the hope of immunization against cancer. The previously mentioned immunization against polyoma virus and its multiple effects is thought to "provide a clue" in the development of a vaccine that is both

polyvalent as to origin and kind of malignancy.[60]

SUMMARY:

The polyoma virus, in summary, has proven to be a provocative discovery. It provides hindsight into the significance of past experimental achievements in carcinogenesis; insight into the individualized situations under which cancer induction is successful; and foresight in converting the tools of experimentally induced viral tumors towards the investigation of human disease.

Only time will reveal the true place of the viral etiology of cancer. A statement made by Peyton Rous in 1936 would fittingly conclude this discussion, "The tumor problem has withstood the most corrosive reasoning. Yet since what one thinks determines what one does in cancer research, as in all else, it is well to think something, and it may prove worthwhile to think one or more tumors of unknown cause are due to viruses."[66]

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