VIRUSES, NUCLEIC ACIDS, AND CANCER

A Collection of Papers Presented at the Seventeenth Annual Symposium on Fundamental Cancer Research, 1963

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Dedicated to the Memory of
Francisco Duran-Reynals, M.D.
(1899–1958)

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Invited Discussants

In addition to the speakers invited to present formal papers at the Symposium and to take part in the discussions, the following individuals were invited as discussants.

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Introduction

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In an attempt to distinguish between the realities and the hypotheses of viral infection as a cause of cancer, the program of this Seventeenth Annual Symposium on Fundamental Cancer Research will be concentrated upon the topic, "Viruses, Nucleic Acids, and Cancer."

There was one man who did much to crystallize earlier work on viruses, to expand and interpret observations on tumor viruses, and to keep alive research on oncogenic viruses during the years when the theory of viral carcinogenesis was in general disfavor throughout scientific communities of the world. Cancer research is indebted to the work of this man, the late Dr. Francisco Duran-Reynals. At least two major theories were introduced by Duran-Reynals. One theory was that the so-called ordinary viruses which induce inflammatory changes are implicated in neoplasia induced by chemical and hormonal carcinogens; another, that the so-called tumor viruses under certain conditions behave like ordinary viruses and induce inflammatory and destructive changes. Because of his brilliant and farsighted experimentation, his lucidity of thought, his logical approach to the problems of cancer research, and his awareness of the distinction between fact and theory, we respectfully dedicate this monograph to our colleague whom we were fortunate to have as participant in our 1957 symposium, the late Dr. Francisco Duran-Reynals.

The first virus-induced tumor described was avian leukosis, as noted in 1908 by Ellermann and Bang. In 1911, Rous reported that avian sarcoma was also of viral origin. The first virus to be obtained in a purified state was the tobacco mosaic agent, successfully isolated in 1935 by Stanley. The isolation of this virus and the ensuing contributions to the knowledge of viral chemical structure have greatly accelerated progress in virology. By 1940, Duran-Reynals had observed that newly hatched chicks could respond to the inoculation of sarcoma virus with a hemorrhagic type of lesion rather than by a neoplastic growth. Gross reported in 1951 that mouse leukemia could

be transmitted by cell-free filtrates injected into newborn mice of a susceptible strain. This fundamental discovery furnished a new incentive for studies on oncogenic viruses. Other pioneers in the discovery and analysis of oncogenic viruses have included Shope, Bittner, Dmochowski, Stewart, Eddy, Beard, Friend, Moloney, and many other researchers.

On the viral theory of carcinogenesis, the late Dr. Charles Oberling could correctly assert in 1944 that the only major disadvantage of the virus hypothesis was that it had not been proved. Between 1944 and 1963, such amazing advances have been made in virology, biochemistry, and related spheres that this statement would no longer be exact.

Parallel to the increasing interest in a possible viral etiology for certain neoplasms, our institution increased its research activities in this area. In a survey reported in 1951, Dr. William Russell summarized recent advances in the development of a viral theory of tumorigenesis, and indicated its potentialities. By 1955, our research program in virology and related fields had expanded sufficiently to allow the establishment of a Section of Virology and Electron Microscopy, headed by Dr. Dmochowski.

The topic of the eleventh in this series of symposia was "Viruses and Tumor Growth." At this 1957 meeting, fundamental discoveries in this rapidly developing area of cancer research were reported, many of them for the first time (Texas Rep. Biol. & Med. 15(3):1–378, Fall, 1957).

Cytochemical and electron microscopic studies have greatly contributed to our knowledge of the structure of viruses and malignant cells. At this institution, in the Section of Electron Microscopy, studies have been made in which the host-virus relationship in polyoma virus of mouse embryo cells was investigated by bright-field, phase, fluorescence, and electron microscopy. At our 1957 symposium, the presence of so-called viruslike particles in cytoplasmic inclusions of cells from the lymph nodes of a patient with acute lymphatic leukemia was first reported. This major contribution to virology was facilitated by electron microscopic techniques. Later, detailed tissue culture studies of human leukemia were also made. Phase-contrast and fluorescence microscopic examination showed that certain sequential, morphologic changes which eventually led to the destruction of the tissue cultures might be associated with a viral agent in the cells of lymph nodes from patients with leukemia or lymphoma. Electron microscope and tissue culture studies of cells derived from cancer eye lesions were also made. Results have suggested that a virus may be associated with bovine ocular squamous carcinoma and its benign precursor. Investigations, such as these, at the levels of fine cellular structure and biochemical interaction at the molecular level are now possible because of highly developed tools such as fluorescent antibody, radioactive tracer materials, and electron microscopy.

Nevertheless, the viral concept of oncogenesis, as it pertains to human cancer, still remains a "working hypothesis." Basic and unanswered questions still hamper access to an ultimate solution of the problem of human neoplasia.

- Do viruses cause all tumors and cancers in animals?
- Are viruses one of the indispensable factors in tumor development, or are they only occasionally one of many factors which are individually responsible for tumor induction?
- What is the chemical composition of tumor viruses, and the structure of oncogenic nucleic acids?
- After a virus or nucleic acid initiates tumor growth, is the presence of either of them in some form necessary for the continued growth of the neoplasm?
- How does the virus development take place?
- Do many or only some of the infectious viruses play a part in the origin of cancer in animals or in man?
- Above all, what and how much can we learn and apply to the problem of human neoplasia from the ever-increasing and fascinating knowledge in the field of bacterial, plant, insect, animal, and human viruses?

These are some of the questions that must be confronted. They are representative of some problems upon which much of cancer research today is focused.

In unnatural hosts, even such well-recognized oncogenic viruses as those of Rous sarcoma, Shope rabbit papilloma, and mouse parotid gland tumors yield tumors in which viruses can no longer be detected. Only the immune response occasionally remains to indicate the viral origin of the tumor. This phenomenon has been variously explained in terms of "masking" of the virus, or as variation in the quantity of active virus. This absence of detectable virus in tumors that are known to be virus-induced was reported by Rous and Murphy as early as 1914, but no definite solutions to the questions evoked by this observation have been forthcoming. However, this phenomenon, on the basis of experimental evidence available to date, could be attributed to a possible modified state of the virus, or, more likely, to the presence of its nucleic acid, at least for the Shope papilloma virus. Therefore, the biochemical aspect is not to be overlooked as a distinct possibility.

Polyoma virus has been shown to contain deoxyribonucleic acid, and infection of cell cultures and induction of hamster tumors with nucleic acid preparations have been reported by DiMayorca and his associates. The recent discovery by Ito that infectious or tumor-inducing nucleic acid can be extracted from rabbit papillomas from which the virus itself no longer can be obtained indicates perhaps one approach to the study of the hypothetical human cancer virus. These exciting discoveries pertaining to viral nucleic acid indicate the possible existence of an immature or incomplete virus-naked viral nucleic acid that is deficient or totally lacking in a protein component. In confirmation of Duran-Reynals' theories and experimental results, other infectious viruses have been shown to act as cocarcinogens, and as direct carcinogens in susceptible hosts, both in vitro and in vivo.

Exciting prospects are foreseeable in future studies on viruses, nucleic

acids, and their relationship to neoplastic processes. A group of proteins, known as interferon, that are capable of inhibiting viral growth are being analyzed to determine whether they can be utilized as antiviral therapeutic agents. Other researchers are attempting to demonstrate a possible parallel between oncogenic viral action and that of the temperate phages. In testing known human viruses for possible oncogenic properties, Trentin, Yabe, and Taylor have recently reported that tissue culture fluid of human adenovirus type 12, injected into hamsters within 24 hours after birth, induced a high incidence of malignant tumors at the injection site within one to three months. Other workers have demonstrated that human adenovirus type 18 has oncogenic activity in newborn hamsters. Further work is required to isolate and purify more oncogenic viruses, to study the epidemiology of human tumors, and to determine the chemical structure of the nucleic acid components of oncogenic viruses.

Viruses have been demonstrated in many hosts and systems, even in tissue cultures, that manifest malignant developments. In order to prove the viral theory of tumor induction, a virus must be regularly isolated, and shown to be proliferative and etiologically related to the tumor from which it has been isolated.

The facts, ideas, theories, and discussions presented at this symposium are intended to converge the various research disciplines upon a common goal . . . the solution of the human cancer problem.

STRUCTURE OF VIRUSES