The Role of Viruses in Human Cancer

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Editors:
Gaetano Giraldo and Elke Beth

THE ROLE OF VIRUSES IN HUMAN CANCER

Proceedings of the First International Congress of Viral Oncology
of the T. and L. de Beaumont Bonelli Foundation for Cancer Research
held in Naples, Italy, September 21–23, 1979

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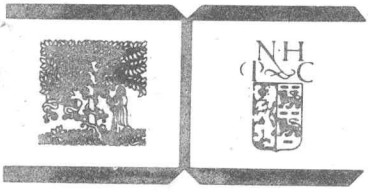

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Preface

This volume is based on the International Congress of Viral Oncology entitled "The Role of Viruses in Human Cancer," held in Naples in September 1979 and sponsored by the de Beaumont Bonelli Foundation for Cancer Research, with the enthusiastic support of Dr. Giulio Tarro, President of the Foundation.

The question of whether viruses cause cancer in man has been asked for twenty years by hundreds of scientists in many laboratories throughout the world. Although we know that viruses do, without doubt, cause various forms of cancer in animals under laboratory and natural conditions, and that specific viral vaccines have been applied in some of them with great success, we still cannot definitely say the same for man, although Epstein-Barr virus appears to be the most probable candidate. Genetic susceptibility, closely associated with immunologic responses, and environmental cocarcinogens are the most prominent features influencing these events. Cancer might be, indeed, the result of multifactorial events in which either heavy perinatal infections or chronic viral infections—like EBV in equatorial Africans or hepatitis B virus—could represent the initiating factor.

The purpose of this conference is to outline the main areas in which viruses can be or have been potentially associated with human malignancies, to draw attention to areas of research such as hepatitis B virus and hepatoma, to learn more about ongoing work on interferon as a possible therapeutic agent, and other new approaches like hybridomas or DNA recombinant technology. Furthermore, the demonstration and biochemical characterization of tumor-specific transplantation antigens (TSTA) might open the way toward a meaningful immunotherapeutic intervention in the control of human cancer.

We are indebted to Dr. Errico di Lorenzo who, in his function as Secretary of the Congress, has contributed significantly to the organization of this meeting. We thank the members of his department for their valuable assistance before and during the meeting. We express our sincere thanks to Ms. Mimi Halpern for her outstanding help and interest in the development of this publication. The cover design was based on a visual impression obtained from a figure kindly provided by the Abbott Laboratories, Diagnostic Division.

Gaetano Giraldo

Elke Beth

Foreword

The acuteness of the cancer problem and the fundamental importance of research aimed at uncovering its causes places the theme of viral involvement in cancer among the most interesting and urgent problems in the field of medical science today.

It is therefore an honor for me and a great privilege to speak about the commitment of the "T. and L. de Beaumont Bonelli Foundation for Cancer Research" in sponsoring the First International Congress of Viral Oncology entitled "The Role of Viruses in Human Cancer." Furthermore, the Foundation wishes to extend this commitment into the future: it is our intention to continue these conferences every three years. The topics to be selected shall cover a wide range and encompass the most up-to-date information on the multifactorial events which lead to cancer in man.

I would like to express my sincere thanks to the members of the Organizing Committee and to all who have contributed with their participation, help and interest in the success of this conference. I am delighted to thank Dr. Denis Burkitt for his participation in the Congress. It was his remarkable detective work and his intuition that opened the way to the discovery of the Epstein-Barr virus and its association with two human cancers—Burkitt's lymphoma and nasopharyngeal carcinoma.

The knowledge we have gained today concerning this virus and its involvement in human malignancies represents one of the most important breakthroughs in the advancement of human cancer research.

Giulio Tarro

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The Background to the Epstein-Barr Virus

Denis P. Burkitt

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Most great things have very small beginnings, and the now world-famous Epstein-Barr virus (EBV), first identified in 1954 by Epstein, Achong and Barr, is no exception.

A Serendipitous Encounter

On March 22, 1961, a little-known surgeon from Africa was to describe one of his research hobbies to the Surgical Department of the Middlesex Hospital Medical School in London. On previous home leaves, he had shared other aspects of his surgical experience in Africa with the Middlesex surgical staff and students. On this occasion he titled his talk "The Commonest Children's Cancer in Tropical Africa. A Hitherto Unrecognized Syndrome."

Something prompted a research virologist, Dr. M. A. Epstein, then working in the adjacent Bland-Sutton Institute, to slip in and sit near the back of this meeting primarily for surgeons.

The lecturer had not been speaking for long before Epstein recognized with a thrill of excitement that the subject being discussed contained the missing clues of the jig-saw puzzle on which he had been working. Here was just the evidence of an epidemiological nature to supplement his experimental studies aimed at showing that viruses could play a causative role in the induction of cancer in man. It had long been known that this was so in a variety of animal species, and although viral agents had not yet been demonstrated to be carcinogenic in humans, why should man differ from animals in this respect?

The evidence that appeared crucial to Epstein's trained and perceptive mind was that the particular form of cancer that the lecturer was describing in Africa had a geographical distribution related to the climatic factors of rainfall and temperature. To him, as to others, this proclaimed a dependence on some biological agent, probably an insect vector that might transmit a virus.

Tony Epstein approached me after the event, for I was the lecturer that day, and requested that I send him fresh tumor tissue removed from my patients in Africa, and offered to be responsible for the cost of transport. He would examine this tissue under the electron microscope for evidence of viral particles. Thus started a fruitful scientific cooperation and a valued personal friendship—and the EBV saga was launched.

As has been described in detail elsewhere, Epstein and his colleagues succeeded where others had failed, by growing the tumor cells in tissue culture before submitting them to electron microscopy.

It must have been some strange perception that perhaps history was being made that prompted Epstein to raise his hand and pull from the notice board the typewritten announcement of my lecture as he left the hall. A replica of this is the first illustration in the recent comprehensive publication, "The Epstein-Barr Virus," which describes the remarkable progress made over the decade and a half since this now famous virus was first observed.[1]

The story following this discovery has been told by others. My role in the drama was drawing to a close. I had been privileged to plant a seed, but had none of the knowledge and expertise required to nurture the plant towards flower and fruit. We each make our particular contribution and then must rejoice to hand the baton on to others. Some brilliant starters may find no one ready to grasp their baton, while hesitant starters may find eager and competent hands to carry their seemingly unremarkable achievements to undreamed-of fruition. So it was in the case of my serendipitous or providential first encounter with Tony Epstein. How did it come to pass that I should be lecturing in London on a children's cancer common in Africa?

The Discovery of a Tumor

One morning well-remembered but naturally not, at the time, recorded, but probably early in 1947, my friend and medical colleague, Dr. H. C. Trowell, then Senior Consultant Physician at Mulago Hospital, Kampala, Uganda, called me in consultation to see a puzzling case. Beginnings of major enterprises have often been insignificant and consequently difficult to date. The patient was a child with swellings in all four jaw quadrants, both sides of his maxilla and both sides of his mandible. This bizarre presentation was not in keeping with sepsis or cancer. I had been aware

of single jaw tumors in children of undetermined nature, but not of multiple simultaneous lesions. A few weeks later when visiting a distant hospital, I found another child with four jaw tumors, and this convinced me that the first was not just a bizarre and unique case. These encounters prompted a careful search for tumors elsewhere in the body in children with jaw lesions, and they were almost invariably discovered. Before long it became increasingly apparent that tumors occurring in characteristic anatomical locations in children tended to be associated with one another in individual patients. The sites most commonly affected were the jaws, the orbit, the kidneys, the liver, the skeleton and, in girls, the ovaries. Moreover tumors in all these sites had a characteristic age distribution, peaking between six and eight years.[2,3]

These observations led to the conviction that rather than these multiple neoplastic deposits being different tumors, they must all be merely differing clinical manifestations of a single tumor. Formerly the orbital lesions were considered retinoblastomas; the ovarian tumors, granulosa-cell tumors; the kidney tumors, neuroblastomas; the long-bone tumors, Ewing's sarcomas—all tumors composed of small round cells.

Subsequently this conclusion, reached by deductive reasoning following clinical observations, was confirmed histologically by O'Conor and Davies,[4] who recategorized all these tumors as a form of lymphoma after review of histological material.

In view of this histological diagnosis, the rarity of peripheral lymph node involvement was particularly puzzling. Subsequently, Wright[5] was to identify the tumor on both histological and cytological criteria as a particular and distinct type of lymphoma.

Geographical Distribution

It soon became apparent that these tumors were by no means equally distributed throughout Uganda, and that they were all common or all rare together in different localities.

A providential visit to Kampala by South Africa's leading cancer epidemiolgist, George Oettlé, provided the opportunity to discuss these tumors with him. A remark of his that these tumors were not seen in South Africa proved seminal, in that it indicated the localized geographical distribution of the disease. This prompted the beginnings of studies throughout Africa, initially by postal questionnaires and subsequently by personal safaris throughout the continent to determine the geographical distribution of the tumor. This was found to consist of a horizontal belt across the continent between 15° North and South of the equator, but with tumor-free areas within this belt, and with a tail running down the east coast as far as the North of Natal.[3,6]

Climatic Dependence

Investigations in South, Central and East Africa revealed that the tumor rarely occurred above an altitude of 5,000 feet above sea level near the equator, above 3,000 feet 1,000 miles South of the equator, or above 1,000 feet further south in Mozambique. This altitude barrier was subsequently recognized to be a temperature barrier, the tumor only being common where the mean daily temperature did not fall below 60°F.[7,8] These studies entailed a 10,000 mile fact-finding tour through much of East, Central and South Africa which reached the pages of Readers' Digest[9] and was the central theme of a book by Bernard Glemser, "The Long Safari".[10]

Later studies in West Africa, a region with great contrasts in rainfall but not, as in East Africa, in altitude, indicated that the tumor rarely occurred where the annual rainfall was below about 20 inches.

The dependence of tumor occurrence on these two climatic parameters suggested the implication of some biological agent. The distribution of this tumor was in fact comparable to that of several known insect-borne diseases.

Viruses are agents which are known to be transmitted by insects, and known, at least in animals, to cause cancer. It was therefore postulated that the tumor being studied might be caused by a vectored virus.

The search for a virus which, as mentioned above, culminated in the identification of EBV, was initiated by a hypothesis which subsequently proved to be false. This virus was found to be ubiquitous, its distribution in no way corresponding to that of the tumor. Yet evidence steadily accumulated implicating this virus in the etiology of what subsequently became known as "Burkitt's lymphoma."

Remarkable Response to Therapy

A factor that added to the interest aroused in this tumor by its epidemiological features was its quite remarkable response to chemotherapy,[11,12] an observation consistent with what had been observed in virus-induced tumors in animals. This was partly explicable by the intense sensitivity of the tumor cells to cytotoxic drugs, and partly to the very strong immunological response mechanisms demonstrated in spontaneous remissions.[13]

Further Encounters with Prof. Epstein

Two further encounters with Professor Epstein deserve comment. It was with him that I realized the hazards often met in research in the tropics. I well remember visiting some islands on Lake Victoria with him in the

hope of persuading local islanders to capture monkeys which could be examined for the presence of viruses. We were conveyed to the islands by motor launch, but for the ten-mile journey to shore long after dark, we had to entrust ourselves to a frail canoe with a temperamental outboard motor. This began to fail shortly after leaving our island and we didn't cherish the prospect of drifting without power in a hippopotamus-inhabited lake subject to sudden violent storms. Fortunately, careful coaxing kept the engine running in spite of many stops and starts, and in total darkness, with no navigational aids, we reached our destination ten miles from our site of departure!

The most recent encounter with Tony Epstein was the happy occasion when I stood before him listening to his oration, a highly embellished account of what this paper has been all about, when he presented me for the Honorary Doctorate in Medicine of Bristol University, where he currently holds the chair in pathology.

How the Eponym Originated

In January 1963, an international conference was held in Paris on the subject of lymphoreticular tumors in Africa. It was largely dominated by the subject "Lymphoma of Children in Africa," and contributions were made by workers in many parts of the continent. There was lack of agreement on the precise nature of the tumor, some participants being unwilling to accept it as a lymphoma. In the absence of any agreed histological terminology, it was agreed to call it Burkitt's tumor, a testimony to the generosity of my colleagues in East Africa who had, with characteristic unselfishness, used this name.[14] Subsequently it was possible to improve on "tumor" and replace this word with "lymphoma." A tumor doesn't necessarily imply cancer, as witness "Pott's puffy tumor."

Later Modification

When searching for an alternative hypothesis that would explain the epidemiological features of Burkitt's lymphoma (BL), an early suggestion by Gilbert Dalldorf was re-examined. He had postulated that the tumor only occurred commonly in regions where malaria was holo- or hyperendemic, which denotes intense transmission throughout the year. The distribution of BL in Africa and parts of Asia was observed to correspond closely to the regions in which malaria is still hyperendemic. The only tumor-free areas in warm, moist parts of Africa were Zanzibar and the environs of Kinshasa—places in which effective malarial control had been maintained. Detailed studies of Uganda showed a close relationship between the prevalence of BL and intensity of malarial infection.

These findings can be explained on the basis that the immunodepres-