

The Role of Viruses in Human Cancer

Vol. 2

Editors:
Gaetano Giraldo and Elke Beth

THE ROLE OF VIRUSES IN HUMAN CANCER

Volume II

Proceedings of the Second International Congress sponsored by the T. and L. de
Beaumont Bonelli Foundation for Cancer Research held in Naples, Italy,
September 22-24, 1983

Editors:

GAETANO GIRALDO and ELKE BETH

Istituto Nazionale Tumori "Fondazione G. Pascale"
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THE ROLE OF VIRUSES IN HUMAN CANCER
Volume II

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PREFACE

The content of the book is based on the Second International Congress entitled THE ROLE OF VIRUSES IN HUMAN CANCER, held in Naples, Italy, September 22-24, 1983, and sponsored by the T. and L. de Beaumont Bonelli Foundation for Cancer Research. The book is dedicated to Dr. Denis P. Burkitt, the recipient of the first 'De Beaumont Bonelli Award for Cancer Research' for outstanding achievements in human cancer research.

The major objective of the book is to present the actual status on the role of viruses in human cancer taking into account achievements, challenges and perspectives. It comprises comprehensive reviews and recent experimental data on oncogenic human viruses, including herpesviruses, hepatitis B virus, papovaviruses and retroviruses, and their potential association with various human malignancies.

The content of several chapters identifies productive interface studies in the furtherance of knowledge in cancer biology and biochemistry by multimodality approaches, current perspectives on multifactorial and multistep carcinogenesis hypotheses proposed for carcinomas in general and their specific fit for certain human cancers. Between the themes reported are: Studies concerning molecular aspects of oncogenic viruses with identification and cloning of viral and cellular oncogenes, their interrelationships, and their gene products *in vitro* and *in vivo* for better understanding of their functions; data evaluation of prospective studies in selected human populations to establish epidemiologic evidence for viral involvement in certain human cancers; current state of malignancy outcome in immunodeficient individuals, particularly in AIDS developing Kaposi's sarcoma; possible therapeutic approaches of cancer by vaccines, interferon and monoclonal antibodies.

Based on informations obtained on viral and cellular oncogenes and their products through DNA recombinant techniques, DNA sequence analyses, transfection experiments and monoclonal antibodies, we are now beginning to realise that in the process of cell transformation viral agents, as chemical and physical ones, are acting through similar steps ending in the activation of cellular oncogenes. At that point, considering oncogenic viruses, the presence of viral markers

(products of their oncogenes) could be no more necessary for the maintenance of cell transformation.

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 also Dr. Emilia Bracco of his department for valuable assistance before and during the meeting.

Gaetano Giraldo

Elke Beth

FOREWORD

In Honour of Denis Burkitt

Modern biomedical science can be said to have had its origins in the Renaissance. During the 16th century it was the great Italian Schools with their studies in anatomy which laid the foundations, and as a result we still today speak of the Fallopian tubes and bursa of Fabricius. As with much else in the Renaissance it took about 100 years for such work to spread to Northern Europe and it was in the 17th century that Niels Stensen in Denmark gave his name to a salivary duct and William Cowper in England to a gland. With the perfection of the achromatic microscope in the 1830s, anatomical studies were extended to tissue components and as a result of pioneer work in Germany we have the loop of Henle in kidney tubules and the giant cells of Langhans in the inflammatory response.

As accurate anatomy, physiology, and histology developed, the definition of clinical conditions became more certain in the 19th century and such giants as Bright, Hodgkin and von Recklinghausen were able to achieve immortality along with many others by delineating and giving their names to diseases. By the 20th century, most of the great descriptions had been made and it has become increasingly unusual for a new and outstanding condition in medicine to be recognised by a single worker, and for that worker to be honoured by the attachment of his name to the syndrome.

Denis Parsons Burkitt is one of the rare individuals in recent years to have made such a contribution and thus to have been accepted throughout the world as an eponym; it is because of his work with the lymphoma which bears his name that he is receiving the Beaumont-Bonelli Award today.

Before going further and considering the importance of Burkitt's Lymphoma I think it might be interesting to see how its discovery came

about. Denis Burkitt was born in February 1911 in Enniskillen, Ulster. The family had a strong tradition both of public service in the British Colonies and India, and of deep Christian faith. Denis Burkitt graduated from Trinity College, Dublin, with the MB Degree in 1935, and three years later took the Fellowship of the Royal College of Surgeons of Edinburgh. From 1941 until 1946 Denis Burkitt was a Surgeon in Britain's Royal Army Medical Corps serving mostly in East Africa with African troops, and then in Ceylon and in liberated Singapore. During his army service he visited Uganda and felt greatly drawn to that country because it was *African* rather than a *settler* country, a difference which even in those days was extremely important. There was also much successful Christian activity in Uganda and when Denis Burkitt was demobilised he decided that his vocation lay there since he felt that he could help the people both medically and spiritually. He joined the Colonial Medical Service and became in Uganda what he has often described as "a simple bush surgeon". There can be no doubt that Denis Burkitt made an important and valuable contribution to the welfare of the Ugandans in this rather humble and undistinguished post, but being the man he is, that was by no means the end of the story. By dint of the true scientific spirit of enquiry and keen observation, Denis Burkitt came to realize in the course of his surgical work that the many seemingly different lymphoid cancers of children in Africa were not disparate entities, but all facets of a single, hitherto unrecognised tumour syndrome, commoner in endemic regions than all other children's cancers added together. It had long been known that various childhood lymphoid tumours were especially frequent in tropical Africa, but although observations on these go back to the very first arrival of missionary doctors, it was not until Denis Burkitt's work that they were recognised as a single disease.

Such a discovery would have been sufficient achievement for most research workers and many have indeed been honoured for comparable findings. However, Denis Burkitt showed himself unique not only in bringing his work to fruition in the most primitive conditions and without any help or back-up, but also by further inspired discoveries. Rightly unsatisfied with descriptive study alone he proceeded to investigate the epidemiology of the tumour. With his first cancer research grant, which added up in total to the amazing sum of

£15 (sterling), Denis Burkitt organized a postal questionnaire throughout sub-Saharan Africa from which, during three years intensive work, he was able to piece together the outlines of the tumour's distribution. Then, with a further research grant - this time the British Medical Research Council actually gave him £250 - and an ancient Ford stationwagon, Denis Burkitt proceeded to drive through East Africa on a 10,000 mile Safari to check the data in person. During this incredible journey he interviewed doctors throughout this portion of the Continent visiting tiny medical missions, village dispensaries, and palm-thatched district hospitals, so that at the end he was able accurately to map the extent of the Burkitt lymphoma belt. From this it became clear that the distribution of the tumour was determined by geographical factors governing temperature and rainfall, and this second contribution has proved of even greater moment. For, a human tumour dependent on climate for its distribution must have some biological agent involved in its cause. By analogy with some animal tumours, a cancer-causing virus was judged from the outset to be the most likely such biological agent, and it is for this reason that Burkitt's lymphoma has proved of such enormous significance as a kind of Rosetta Stone for human tumour virology.

All this was achieved while at the same time ministering as a skilled surgeon to the needs of a population largely lacking even rudimentary medical care. Denis Burkitt progressed from Government Surgeon in the Colonial Medical Service to be a lecturer in Surgery at Makerere University Medical School in Kampala, and was later promoted to Senior Consultant Surgeon to the Uganda Ministry of Health. He left Uganda shortly before independence and continued his geographical pathology studies in London as a member of the External Scientific staff of the Medical Research Council, and has in recent years become eminent again for his widely-known advocacy of high residue diet as an alleviator of many of Western man's ills.

I have told you about Dr Burkitt's progress through his career. Now I must add a word about the reactions of the world of science to his contributions. In 1964 the Harrison Prize from the Royal Society of Medicine; in 1966 the Stuart Prize from the British Medical Association; in 1968 the Arnott Gold Medal of the Irish Hospitals and Medical Schools Association; in 1969 the Katherine Berkan Judd Award of the Sloan

Kettering Institute, New York; in 1970 the Robert de Villiers Award of the American Leukaemia Society; in 1971 the Walker Prize from the Royal College of Surgeons of England; in 1972 the Paul Ehrlich Ludwig-Darmsdaeter Prize and Medal, the London Society of Apothecaries Gold Medal, and the Albert Lasker Clinical Chemotherapy Award; in 1973 the Gairdner Foundation Award; in 1978 the Gold Medal of the British Medical Association; in 1982 the Bristol Myers Award and the General Motors Mott Prize; and in 1983 the Gold Medal of the French Académie de Médecine - each of these a major scientific accolade, and to match this catalogue let me tell you of the honours he has received from Academic bodies. An Honorary DSc Degree of the University of East Africa in 1970; Fellowship of the Royal Society in 1972; Honorary Fellowship of the Royal College of Surgeons of Ireland in 1973; Honorary Fellowship of the Royal College of Physicians of Ireland in 1976; an Honorary MD Degree of the University of Bristol in 1979; and an Honorary DSc Degree of the University of Leeds in 1982. He has been made an Honorary Fellow of the East African Association of Surgeons, of the Brazilian Society of Surgery, of the Sudan Association of Surgeons and of the International Medical Club of Washington. In 1970 Her Majesty the Queen made him a Companion of the Order of St Michael and St George.

Each contribution from Denis Burkitt has revealed his astonishing powers of observation and the originality with which he has recognised simple things and developed them to make concepts of outstanding significance. Each innovative idea has provided a step forward of great importance in medical and biological science. It is a privilege for me to welcome Denis Burkitt before you here, as we join other distinguished institutions and groups in honouring him. I have much pleasure in presenting to you Denis Parsons Burkitt as eminently worthy of the Beaumont-Bonelli Award for Cancer Research.

M. A. Epstein

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CONTENTS

Preface	ix
Foreword	xi
Participating contributors and chairmen	xv
Possibilities and priorities of cancer prevention Denis P. Burkitt	1
The functional organization of the herpes simplex virus genomes Bernard Roizman	11
Herpes simplex virus and ocular disease Ysolina M. Centifanto-Fitzgerald	25
Role of the promoter sequence of the thymidine kinase gene of HSV-1 in biochemical transformation of cells, gene expression and neurovirulence in mice Yechiel Becker, Yehuda Shtram, Avner Barasofsky, Michelle Haber, Annie Scemama, Yael Asher, Eynat Tabor, Tamir Ben-Hur, Donald Gilden and Julia Hadar	37
Molecular biology of the relationship between herpes simplex virus-2 and cervical cancer James K. McDougall, Patricia Smith, Hisham K. Tamini, Ernest Tolentino and Denise A. Galloway	59
HSV-2 and cervical cancer: The transformation lesson Laure Aurelian, Mark M. Manak and P.O.P. Ts'o	73
Antiviral chemotherapy Herbert E. Kaufman and Emily D. Varnell	87
Epstein-Barr virus and Burkitt's lymphoma M.A. Epstein	93
Latent infection and growth transformation by Epstein-Barr virus Elliott Kieff, Timothy Dambaugh, Kevin Hennessy, Susan Fennewald, Mark Heller, Takumi Matsuo and Mary Hummel	103
Epstein-Barr virus - Oncogenesis in immune deficient individuals David T. Purtilo	119
Association of EBV with some carcinomas originating in Waldeyer ring outside nasopharynx B. Břicháček, I. Hirsch, A. Suchánková, E. Vilikusová, O. Šíbl, H. Zavadová and V. Vonka	137
EBV associated membrane antigens on virions, producer cells and trans- formed lymphocytes David A. Thorley-Lawson	153

VI

The molecular biology of human cytomegalovirus and its relationship to various human cancers Eng-Shang Huang, Istvan Boldogh, John F. Baskar and Eng-Chun Mar	169
The significance of interferon in serum of patients with acquired immune deficiency syndrome and of persons at risk Elena Buimovici-Klein, Michael Lange, Richard J. Klein, Michael H. Grieco and Louis Z. Cooper	195
Diagnosis and prevention of human cytomegalovirus infections Max A. Chernesky	201
Woodchuck hepatitis virus-induced hepatomas contain integrated and closed circular viral DNAs Jesse Summers, C. Walter Ogston, Gerald J. Jonak, Susan M. Astrin, Gail V. Tyler and Robert L. Snyder	213
Hepatitis B virus infection and hepatocellular carcinoma - Perspectives for prevention Alain Goudeau, Bernard Yvonnet, Francis Barin, Francois Denis, Pierre Coursaget, Jean-Paul Chiron and Ibrahima Diop Mar	227
Prevalence and significance of antibody against an antigen (HBV/T Ag) present in a human hepatoma cell line carrying integrated hepatitis B virus DNA Francis Barin, Gerald Lesage, Jean-Loup Romet-Lemonne and Alain Goudeau	239
Experimental oncogenicity by human papovaviruses and possible correlations with human tumors Giuseppe Barbanti-Brodano, Alfredo Corallini and Maria Pia Grossi	249
SV40 in human brain tumors: Risk factor or passenger? Erhard Geissler, Siegfried Scherneck, Helmut Prokoph, Wolfgang Zimmermann and Wolfhard Staneczek	265
Plasma membrane-bound M _p 94 000 simian virus 40 and BK virus tumor antigens act as cross-reacting tumor specific transplantation antigens Rupert Schmidt-Ullrich, Elke Beth and Gaetano Giraldo	281
Avian sarcoma virus and Koch's postulates in human viral oncology G.F. Rabotti, B. Teutsch, J. Auger, F. Mongiat and M. Mariller	293
Retrovirus-induced leukemias of animals and humans William D. Hardy, Jr.	311
Adult T-cell leukemia virus: An outlook Yorio Hinuma	331
Viruses in human leukemia Abraham Karpas	345
The etiology of human breast cancer: Related viral and non-viral antigen expression in mammary tumors of mice and man Nurul H. Sarkar	365

Interferon and human cancer Gabriel Emödi	387
Ataxia-telangiectasia - A human autosomal recessive disorder predisposing to cancer Yechiel Becker, Meira Shaham, Eynat Tabor and Yosef Shiloh	397
Summing up Bernard Roizman	407
Author index	411
Subject index	413

POSSIBILITIES AND PRIORITIES OF CANCER PREVENTION

DENIS BURKITT

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INTRODUCTION

Modern scientific medicine is too prone to consider man as a machine. When some component of the machine functions badly the approach to the problem is focused almost exclusively on identification of the fault, representing medical diagnosis, and on efforts to repair, as far as possible, the defective part, the counterpart of treatment. Hardly a thought is given to the possibility that malfunction of the machine may be caused by the environment in which it operates, and consequently no serious effort is made to rectify this all-important factor. The machine is left out in the rain or snow, surrounded by skilled mechanics who are elaborately equipped, so intent on their job that the thought never crosses their mind that the machine might run better if protected from the elements.

I do not believe this picture to be an exaggeration of the overwhelming preponderance of effort and expenditure currently devoted to the diagnosis and treatment of disease, including cancer, relative to the low priority given to preventive measures. This in spite of the fact that it is now generally accepted that environmental factors are of paramount importance in the causation of most disease, and not least in the case of cancer. Early detection is often of greater prognostic significance than is the choice of therapeutic procedures, but prevention is of incomparably greater value than is early diagnosis or skilful therapy.

In that highly authoritative document "Nutrition and Cancer"(1) it was stated "It is highly likely that the United States will eventually have the option of adopting a diet that reduces the incidence of cancer by approximately one-third, and it is absolutely certain that another third could be prevented by abolishing smoking."

Knowledge now available makes it clear that several of the commonest cancers in the world, together making up a considerable proportion of the whole, are likely soon to be potentially