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General Editors: A. Canonico, O. Estevez, R. Chacon and S. Barg

Volume I

Carcinogenesis

Editor: G. P. Margison

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Proceedings of the 12th International Cancer Congress, Buenos Aires, 1978

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CARCINOGENESIS

Editor:

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XII - ABSTRACTS

(Each volume is available separately.)

Foreword

This book contains papers from the main meetings of the Scientific Programme presented during the 12th International Cancer Congress, which took place in Buenos Aires, Argentina, from 5 to 11 October 1978, and was sponsored by the International Union against Cancer (UICC).

This organisation, with headquarters in Geneva, gathers together from more than a hundred countries 250 medical associations which fight against Cancer and organizes every four years an International Congress which gives maximum coverage to oncological activity throughout the world.

The 11th Congress was held in Florence in 1974, where the General Assembly unanimously decided that Argentina would be the site of the 12th Congress. Argentina was chosen not only because of the beauty of its landscapes and the cordiality of its inhabitants, but also because of the high scientific level of its researchers and practitioners in the field of oncology.

From this Assembly a distinguished International Committee was appointed which undertook the preparation and execution of the Scientific Programme of the Congress.

The Programme was designed to be profitable for those professionals who wished to have a general view of the problem of Cancer, as well as those who were specifically orientated to an oncological subspeciality. It was also conceived as trying to cover the different subjects related to this discipline, emphasizing those with an actual and future gravitation on cancerology.

The scientific activity began every morning with a Special Lecture (5 in all), summarizing some of the subjects of prevailing interest in Oncology, such as Environmental Cancer, Immunology, Sub-clinical Cancer, Modern Cancer Therapy Concepts and Viral Oncogenesis. Within the 26 Symposia, new acquisitions in the technological area were incorporated; such acquisitions had not been exposed in previous Congresses.

15 Multidisciplinary Panels were held studying the more frequent sites in Cancer, with an approach to the problem that included biological and clinical aspects, and concentrating on the following areas: aetiology, epidemiology, pathology, prevention, early detection, education, treatment and results. Proferred Papers were presented as Workshops instead of the classical reading, as in this way they could be discussed fully by the participants. 66 Workshops were held, this being the first time that free communications were presented in this way in a UICC Congress.

The Programme also included 22 "Meet the Experts", 7 Informal Meetings and more than a hundred films.

METHODOLOGY

The methodology used for the development of the Meeting and to make the scientific works profitable, had some original features that we would like to mention.

The methodology used in Lectures, Panels and Symposia was the usual one utilized in previous Congresses and functions satisfactorily. Lectures lasted one hour each. Panels were seven hours long divided into two sessions, one in the morning and one in the afternoon. They had a Chairman and two Vice-chairmen (one for each session). Symposia were three hours long. They had a Chairman, a Vice-chairman and a Secretary.

Of the 8164 registered members, many sent proferred papers of which over 2000 were presented. They were grouped in numbers of 20 or 25, according to the subject, and discussed in Workshops. The International Scientific Committee studied the abstracts of all the papers, and those which were finally approved were sent to the Chairman of the corresponding Workshop who, during the Workshop gave an introduction and commented on the more outstanding works. This was the first time such a method had been used in an UICC Cancer Congress.

"Meet the Experts" were two hours long, and facilitated the approach of young professionals to the most outstanding specialists. The congress was also the ideal place for an exchange of information between the specialists of different countries during the Informal Meetings. Also more than a hundred scientific films were shown.

The size of the task carried out in organising this Congress is reflected in some statistical data: More than 18,000 letters were sent to participants throughout the world; more than 2000 abstracts were published in the Proceedings of the Congress; more than 800 scientists were active participants of the various meetings.

There were 2246 papers presented at the Congress by 4620 authors from 80 countries.

The Programme lasted a total of 450 hours, and was divided into 170 scientific meetings where nearly all the subjects related to Oncology were discussed.

All the material gathered for the publication of these Proceedings has been taken from the original papers submitted by each author. The material has been arranged in 12 volumes, in various homogenous sections, which facilitates the reading of the most interesting individual chapters. Volume XII deals only with the abstracts of proffered papers submitted for Workshops and Special Meetings. The titles of each volume offer a clear view of the extended and multidisciplinary contents of this collection which we are sure will be frequently consulted in the scientific libraries.

We are grateful to the individual authors for their valuable collaboration as they have enabled the publication of these Proceedings, and we are sure Pergamon Press was a perfect choice as the Publisher due to its responsibility and efficiency.

Argentina
March 1979

Dr Abel Canónico
Dr Roberto Estevez
Dr Reinaldo Chacon
Dr Solomon Barg

General Editors

Introduction

In this volume, the integration and expression of the viral genome and the role of virus and antiviral immunity in malignant transformation is examined in studies which have involved cells in culture and laboratory, and domestic animals together with normal or mutant animals or human viruses. Such approaches will help to establish whether human leukemia or other human neoplasms have a viral etiology.

Epidemiological data continue to provide the only conclusive evidence that environmental agents such as chemicals and various types of physical agents induce cancers in man. However, both cell culture and animal experiments are essential if the mechanisms of action of such agents is to be elucidated. In addition, a number of test systems, principally employing cultured cells, have been proposed as rapid screening procedures for detecting chemicals which may be potentially carcinogenic. These experimental systems can make an important contribution to the identification and eventual elimination of carcinogens from the environment.

March 1979 G. P. MARGISON

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Bioassay Systems for Carcinogenesis

Viral Oncogenesis and Comparative Leukemia

Summary

Dr. Prakash Chandra reported that RNA-dependent DNA polymerase activity with biochemical properties resembling polymerase, associated with retroviruses, has been purified from: 1) human spleen of a patient with myelofibrosis; 2) granulocytic sarcoma (orbital tumor) associated with acute myelomonocytic leukemia in Turkish children; and 3) human primary melanoma tissue.

Serological studies provided evidence that reverse-transcriptase (rt) from human spleen is not antigenically related to cellular DNA polymerase-α, -β or -γ, but is antigenically related to DNA polymerase from simian sarcoma virus (SiSV) and gibbon-ape leukemia virus (GaLV). Similarly, the orbital rt activity was strongly inhibited by antibodies to DNA polymerase from GaLV. Antibodies to DNA polymerases from non-primate sources failed to inhibit the rt activity purified from human spleen or from the orbital tumor. Surprisingly, the activity of human melanoma rt was not inhibited by antisera to rt from SiSv, GaLV and myelofibrotic spleen. Antibodies against purified DNA polymerases from baboon endogenous virus (BEV) and rhabdomyosarcoma virus (RD-114) neutralized the rt activity from human melanoma tissue to almost 80%. The antisera to the enzymes inhibited the human melanoma enzyme almost as effectively as they inhibited their homologous enzymes.

Jes Forchhammer and Jes Klarlund presented their recent results on "Changes in proteins from transformed cultures and tumors induced by sarcoma virus." Their approach was to study cellular proteins by two-dimensional gel electrophoresis using Moloney sarcoma virus and a temperature-sensitive (ts) mutant of this virus. In tissue culture, they consistently found disappearance of a nuclear protein (MW 33 kd, pI 4.8) in the transformed state, which they termed nuclear transformation sensitive protein (NUTS).

Furthermore, they introduced a novel method of studying ts-functions *in vivo*. They injected virus into the tail tissue of mice, and by keeping the mice at different temperatures, they could reproduce permissive and non-permissive temperatures *in vivo*, i.e., tumors only formed at the permissive temperature with the ts-mutant. By labeling whole mice with ^{35}S-methionine and extracting proteins from tails with or without tumors they showed that the "NUTS" protein was absent in tumors but present in extracts from mice injected with the ts-mutant which was kept at the non-permissive temperature. This approach should be applicable to other tumor virus ts mutants, thus reducing the gap between transformation studies in tissue culture and studies of tumors *in vivo*.

Summary

Dr. Robert Gallo reported that there is substantial evidence for specific sarcoma virus genes, i.e., a gene of a sarcoma retrovirus which codes for protein(s), involved in transformation. There are recent claims that the "sarc" gene product has been identified. It is less certain that leukemia viruses cause leukemia by providing a "leuk" gene. He emphasized that the known causes of naturally occurring leukemia (of a major fraction of leukemic cases of an animal population) involve viruses (chickens, wild-type mice, cats, cows, and gibbon apes). In each there is abundant replicating retrovirus while in other species with leukemia little or no virus may be found. He proposed that these animals may be exceptions, not in having viruses involved in the cause of their leukemias, but in tolerating such extensive virus replicaion. Virus involvement in leukemia may involve minimal virus replication with only fragments of viral sequences integrated into the host cell DNA or may involve an indirect effect of the virus. Many cats with leukemia (about 1/3) are virus negative (-), yet the cause of the leukemia still appears to be feline leukemia virus (FeLV). Moreover, he has not found any differences in proviral sequences of tissues of virus positive (+) leukemic cats compared to virus (+) normal cats or between virus (-) leukemic cats and virus (-) normal cats. Thus, in this case the effect of virus could be indirect or involves minor differences in the provirus state (e.g., positional or minor fragments). That fragments of provirus can integrate into host DNA is indicated by recent results from his laboratory with a gibbon naturally infected by gibbon ape leukemia virus (GaLV). In this animal, virus could not be isolated, conventional hybridization gave marginal results for presence of provirus, but restriction enzyme digestion followed by blot hybridization demonstrated an integrated fragment of GaLV. GaLV is closely related to the woolly monkey (simian) sarcoma virus (SiSV). This virus group is of interest because its members are the only primate retroviruses which are known to cause disease and they can affect growth and differentiation of human blood cells. Also, some results suggested that viruses or subviral molecules related to SiSV may be present in humans. Recently, while surveying human DNA for viral sequences by restriction enzyme analysis and blot hybridization, he found a fragment which specifically hybridizes to the RNA genome of SiSV. This fragment: (1) appears to be related to part of the SiSV genome, (2) was detected with several endonucleases, (3) has been found in all human DNA, (4) appears to be in multiple copies, and (5) can be pseudotyped. This fragment has the properties of an endogenous virogene. Studies are in progress to determine if it has any relation to cell growth.

Dr. Harald zur Hausen summarized knowledge concerning the properties of human papova and papilloma viruses. He stressed that there are a number of types based on criteria established by nucleic hybridization tests and that certain human conditions were more regularly associated with some of the viruses being characterized than with others.

Dr. Fred Rapp discussed the properties of human herpesviruses, especially herpes simplex (HSV) and cytomegalovirus (CMV). These are double-stranded DNA-containing viruses that have the ability to infect a host, to cause overt disease, to infect a host and enter a state of latency, and sometimes, as a rare event, to cause oncogenic transformation of a cell. Naturally-occurring neoplasias, such as renal adenocarcinomas of Leopard frogs and lymphomas in chickens, prompted investigations of the human herpesviruses to determine whether any of these viruses are involved in the etiology of cancers in humans. Of the five known human herpesviruses, herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV), only HSV-2, EBV and, more recently, CMV have been associated with cancers in humans thus far. Transformation studies using herpes simplex virus types 1 and 2 and cytomegalovirus have established that these viruses are capable of converting normal cells into malignant cells.

Co-factors can act synergistically to yield higher transformation frequencies in a quantitative assay using the enzyme, thymidine kinase as a marker. Whether these viruses actually play a role in the development of malignant disease in humans has not yet been definitively established.

Dr. Klaus Munk noted that the prerequisite for all transformation experiments with viruses is the establishment of a non-permissive or a non-productive virus host cell system. He has established a non-permissive host cell system which allows the utilization of wild-type HSV. He used a supra-optimal incubation temperature of 42°C or alternatively the sub-optimal incubation temperature of 20°C for a certain period of incubation time. From both types of experiments he obtained transformed cell lines which met all requirements of a neoplastically transformed cell including the ability to grow into malignant tumors after injection of these cells into isogenic animals (Sprague-Dawley rats). In addition, the HSV-transformed rat cells grew rapidly with altered morphology, had a higher plating efficiency than untransformed cells, formed colonies in soft agar, and the modal number of chromosomes was greater than 42.

Overall, the Symposium demonstrated the rapid accumulation of data concerned with the oncogenic properties of mammalian viruses and gave promise that the association of these viruses with naturally occurring neoplasias, including those of man, will be greatly strengthened in the near future.