Biology of Radiation Carcinogenesis

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（内部交流）

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Raven Press • New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

International Standard Book Number 0–89004–010–9
Library of Congress Catalog Card Number 74–14486

Preface

Society-at-large has been, and will continue to be, exposed to minute doses of ionizing radiation, the major potential hazard of which is the induction of cancer. With the exception of military applications, each type of exposure is an unwanted by-product of some beneficial application of technology, e.g., medical diagnostics and treatment, energy production, etc., and judgments must be made as to whether the benefits obtained offset the risk involved. Clearly, it is impossible to observe the effects of minute doses of radiation in the laboratory, as the experimental sample sizes are beyond the scope of even the largest animal facilities.

It is likely, however, that the effects of minute doses of radiation can be predicted, if the mechanisms involved are completely understood. Toward this end, scientists from a variety of disciplines met in Gatlinburg, Tennessee in April 1975 in the hope of providing a complete understanding of this complex problem.

In contrast to previous works on the subject, this volume, which is based on that symposium, is concerned not with description of empirical facts, but rather with an analysis of the mechanisms involved. Throughout the book, the point is made that a rational prediction of potential hazards to man can only be made if a complete understanding of the mechanisms involved is at hand. Six levels of organization have been included in this survey: molecular, genetic, viral, cellular, intercellular, and population. These categories are somewhat arbitrary, as most of the contributions span more than a single level.

This book is concerned specifically with radiation; however, through a comparison of radiation with other carcinogens the contributors have developed an up-to-date summary of carcinogenesis in general. The book therefore describes not only what we do know with regard to carcinogenesis, but perhaps more importantly what we do not know.

Although a final resolution of this problem remains elusive, the data presented by each contributor have completed a portion of the puzzle, and have indicated that, with continued effort, The Biology of Radiation Carcinogenesis will be resolved. This publication will be of interest to oncologists in general, and to health physicists, radiation therapists, radiation biologists, virologists, and nucleic acid biochemists.

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(June 1975)

Acknowledgments

The editors are indebted to the following for their help in organizing and running the symposium on "The Biology of Radiation Carcinogenesis": Drs. H. I. Adler (ORNL), A. Hollaender (ORAU), and J. Miller (U. of Wisc.), members of the organizing committee; Drs. M. Elkind (ANL), C. Heidelberger (U. of Wisc.), R. B. Setlow (BNL), A. Girardi (ETCRC), members of the program committee; and Drs. J. B. Storer (ORNL), R. B. Setlow (BNL), H. S. Kaplan (Stanford), M. Elkind (ANL), A. Girardi (ETCRC), and C. Heidelberger (U. of Wisc.); and Mary Jane Loop and Charles Normand, who took care of everything else.

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Introduction

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It is interesting to note that general concern over the health hazards of ionizing radiation has shifted during the past years from its genetic effects to its somatic effects—notably, tumor induction or carcinogenesis. One reason for this change in emphasis has been, no doubt, new scientific information on increased incidence of tumors, notably of the female breast and of the thyroid gland, in humans exposed to doses of radiation below the level that was previously thought to be carcinogenic. Furthermore, the unprecedented efforts presently being made under the National Cancer Program in the United States have focused attention on cancer, in general, and on factors that increase its incidence, including ionizing radiation.

Whatever the reasons, the practical questions that have to be answered concern estimates of the increase in tumor incidence following relatively low doses of radiation, in much the same way that genetic hazards have been evaluated previously. Even in rodents, we cannot hope to measure directly the increase in tumor incidence that is associated with doses of the order of 1 rad/year or less, so that extrapolations will have to be made from higher dose levels, on which data are already available or can be obtained in the foreseeable future. These extrapolations will of necessity be performed over a broad range, i.e., from doses of the order of hundreds of rads per year down to 1 rad/year or even lower. Actually, such extrapolations should be termed predictions, and the only way by which these predictions can obtain reliability is to base them on a demonstrated knowledge of the mechanisms involved in the induction of tumors by ionizing radiation. It was therefore highly appropriate that the organizers of the 1975 Gatlinburg symposium selected as their topic "The Biology of Radiation Carcinogenesis," and by their choice of speakers have focused on furthering our understanding of the processes that occur between the impact of the radiation itself and the occurrence of a measurable tumor mass. From that stage onward, the processes that take place are becoming better understood every day, because they can be analyzed by better and better methods, from the point of view of the tumor growth itself as well as the reactions to the tumor that occur in the tumor bearer.

With regard to the description of the carcinogenic process itself, it seems

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advisable to distinguish two stages—the first one ending with the occurrence of one or more transformed cells, with the property of unlimited and uncontrolled proliferation, the second one being the proliferation of these transformed cells into a clinically detectable tumor mass. The 1975 Gatlinberg symposium was primarily concerned with the first stage, that is, the transformed cell, as defined above, was the end point of most of the discussions.

The pathway by which the carcinogenic process occurs, following irradiation, seemed to have a number of recognizable cornerstones when the symposium started, at least in the mind of the author. It was understood that specific viruses play an essential role in the induction of some tumors by ionizing radiation. Many animal tumors can be evoked by the action of viruses on cells, and in certain cases of radiation-induced tumors, such as the lymphomas that follow fractionated irradiation of C57BL mice and the osteosarcomas of mice, a virus has indeed been isolated from the irradiated tissues or from the tumor itself and has been shown to induce tumors in unirradiated animals.

It was known that many tumor cells carry either abnormal numbers of chromosomes or characteristic aberrant chromosomes, or both, but these features did not seem to have a special significance in uninhibited growth. Also, evidence seemed to be accumulating in favor of an indirect mechanism of transformation, one that involved the transfer of genetic materials from one cell to another. Furthermore, active DNA synthesis, be it during normal duplication or duplication during the repair of radiation-induced lesions, was required for the cells to undergo transformation. The consequence of the latter mechanism could be an increased incidence of transformations following increased opportunities for repair, such as occur with fractionated irradiation. Such observations had been reported for transformation of cells *in vitro* by fractionated doses of X-rays.

It became clear from this Gatlinburg symposium, in which these issues and others were dealt with in depth, that the relevance of all of these points must be critically reconsidered. The causative role of radiation leukemia virus in radiation lukemogenesis was questioned by the same investigators who discovered the virus and described its role more than a decade ago. New and exciting evidence was provided from work with somatic cell hybrids in favor of the specific involvement of one human chromosome coding for the transformation of a tumorigenic phenotype. With regard to the effects of split versus single doses of ionizing radiation, it became evident from the presentations and the subsequent discussions that scoring of transformed cells *in vitro* might yield different results than the results obtained from scoring tumors *in vivo*. As was pointed out by one of the organizers of the symposium upon which this volume is based, different experimental systems and conditions seem to provide us with different answers, and, from all of these seemingly conflicting data, we must derive the main mechanisms of the carcinogenic process.

A great deal of effort has been exerted world-wide in the study of the carcinogenic effects of radiation, viruses, and chemical agents. It is becoming