FREDERICK F. BECKER, EDITOR

CANCER

A COMPREHENSIVE TREATISE

1

ETIOLOGY: Chemical and Physical Carcinogenesis

SECOND EDITION

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ETIOLOGY: Chemical and Physical Carcinogenesis

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ETIOLOGY: Chemical and Physical Carcinogenesis

Volume 1 • ETIOLOGY: Chemical and Physical Carcinogenesis

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Volume 2 • ETIOLOGY: Viral Carcinogenesis

Volume 3 • BIOLOGY OF TUMORS: Cellular Biology and Growth

Volume 4 • BIOLOGY OF TUMORS: Surfaces, Immunology, and Comparative Pathology

Volume 5 • CHEMOTHERAPY

Volume 6 • RADIOTHERAPY, SURGERY, AND IMMUNOTHERAPY

To Mary Ellen Becker

without whose encouragement and support
this treatise would not have been completed.

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to Volume 1

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Preface

Six years ago when the first edition of this volume appeared as the first of the series, questions were posed in its preface that are as valid today as they were then. In that preface, I proposed the following challenges:

> (1) We must identify carcinogenic agents, and by an analysis of their "nature," e.g., structure and physical characteristics, we may better understand their mechanism of action. (2) We must identify crucial interactions between these carcinogens and important macromolecules within the cell, distinguishing those which relate to carcinogenesis from those which are extraneous. (3) We must examine the alterations of cell function induced by these reactions, for it is with an understanding of phenotypic variation that we may know why malignant cells escape from normal homeostatic control. (4) Last, and perhaps of greatest importance, we must define malignancy—define those characteristics of cellular activity that permit the malignant cell to compete so effectively with the normal constituent, which ultimately leads to such destructive events.

Although great strides have been made toward those goals, as evidenced by a number of new chapters and the new information gathered into others, and although the achievement of those goals sometimes appears but a tantalizing experiment away, none have been achieved. For example, several chapters include descriptions of the progress that has been made toward the development of "quick assays." The aggregate of methods they describe is aimed at making available a test or cascade of tests that, in a short time and for reasonable cost, will indicate with a high probability of accuracy whether a given chemical agent would be carcinogenic for man. The socioeconomic implications of such tests should be all too familiar to the reader. In the main, these tests extrapolate from mutation or other cellular alteration to carcinogenicity. By implication, they can cause chemicals of value to be proscribed or they can justify the persistence of a carcinogen in our environment. Additionally, these tests, which utilize organisms ranging from the lowest forms of prokaryotes to human cells in aggregate, may yield information about the type of basic alteration responsible for the initiation (in the broadest sense) of the carcinogenic process.

The overlap of these findings with those described by Rajalakshmi and others is evident. An enormous amount of information has emerged concerning the nature and specificity of intracellular macromolecular interactions by these agents. Their "imprinting" on the cell's genome, the balance of repair and

misrepair, the magnification of the alteration by cell division, and other cellular phenomena are becoming more apparent. Yet all these findings, as well as those of the quick assays, have not answered the pertinent questions: Is DNA alteration obligate in the process? What is the nature of that change induced by agents totally different in their macromolecular interaction that results in malignancy? How is that change induced?

Berenblum, Farber, and others elaborate on the sequences of cellular alteration required for the development of the carcinogenic process. These presentations demonstrate great progress in our attempts to learn the sequence of carcinogenesis. But they also elucidate the second great question in this field, the nature of the cellular alterations induced by the initial changes that evoke malignant behavior. We have come far since Warburg's hypothesis on the nature of the underlying cellular metabolic alterations, and indeed, interest in that hypothesis has appeared again. Still, the obligate cellular alterations remain unknown.

Thus, it should be no surprise that the most important of all the questions that remain unanswered is, what is malignancy?

It has been proposed that if we could identify all the environmental causes of cancer and remove them or modify their effects (with the so-called chemoprotective agents), we could eliminate malignancy. However, we have become increasingly aware that problems in the environment are not simply due to contamination by chemicals (see Becker), and even the most optimistic enthusiast does not envision agents to protect us totally against our environment. The cancer therapist puts forth the thesis that once a "general" cure is found, concern, and indeed experimentation, in the field can cease. However, if we have learned any single lesson in the last half decade, it has been that these studies have enormous potential beyond understanding cancer. Aging, genetic diseases, and many other problems apparently overlap in cause and potential remedies.

More important is the strong possibility that the basic experiments to which I referred above will lead to the final eradication of this dread condition. The cure will be *knowledge*! Thus, while the optimism in each approach can help sustain its protagonists, we must not let this surety place us in adversarial roles. The most certain contribution to the future, to cancer's elimination and to our general understanding of disease, is an understanding of the processes that establish and maintain the normal function and health of the cell.

F.F.B.

Houston

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