CANCER 1

A COMPREHENSIVE TREATISE

ETIOLOGY: Chemical and Physical Carcinogenesis

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FREDERICK F. BECKER, EDITOR
New York University School of Medicine

PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

Becker, Frederick F.
Etiology—chemical and physical carcinogenesis.

(His *Cancer, a comprehensive treatise;* v. 1)
Includes bibliographies and index.
1. Carcinogenesis. I. Title.
[DNLM: 1. Neoplasms. QZ200 B397c]
RC261.B42 vol. 1. [RC268.5] 616.9'94'008s
ISBN 0-306-35201-X [616.9'94'071] 74-31195

A Division of Plenum Publishing Corporation
227 West 17th Street, New York, N.Y. 10011

United Kingdom edition published by Plenum Press, London
A Division of Plenum Publishing Company, Ltd.
4a Lower John Street, London W1R 3PD, England

Printed in the United States of America

Contributors

to Volume 1

ROBERT W. BALDWIN, Cancer Research Campaign Laboratories, University of Nottingham, Nottingham, England

ISAAC BERENBLUM, The Weizmann Institute of Science, Rehovot, Israel

K. GERHARD BRAND, Department of Microbiology, University of Minnesota Medical School, Minneapolis, Minnesota

EMMANUEL FARBER, Fels Research Institute and Department of Pathology, Temple University School of Medicine, Philadelphia, Pennsylvania

JACOB FURTH, Institute of Cancer Research and Department of Pathology, Columbia University College of Physicians and Surgeons, New York, New York

W. E. HESTON, Laboratory of Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

ALBRECHT M. KELLERER, Department of Radiology, Columbia University College of Physicians and Surgeons, New York, New York

ALFRED G. KNUDSON, JR., The University of Texas Health Science Center at Houston, Graduate School of Biomedical Sciences, Houston, Texas

CORNELIS J. M. MELIEF, Hematology Service, New England Medical Center Hospital, and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

PETER C. NOWELL, University of Pennsylvania, Philadelphia, Pennsylvania

MICHAEL POTTER, National Cancer Institute, Leukemia Studies Section, Bethesda, Maryland

MICHAEL R. PRICE, Cancer Research Campaign Laboratories, University of Nottingham, Nottingham, England

S. RAJALAKSHMI, Fels Research Institute and Department of Biochemistry, Temple University School of Medicine, Philadelphia, Pennsylvania

JANARDAN REDDY, Department of Pathology, University of Kansas Medical Center, Kansas City, Kansas

HARALD H. ROSSI, Department of Radiology, Columbia University College of Physicians and Surgeons, New York, New York

D. S. R. SARMA, Fels Research Institute and Department of Pathology, Temple University School of Medicine, Philadelphia, Pennsylvania

ROBERT S. SCHWARTZ, Hematology Service, New England Medical Center Hospital, and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

JOHN B. STORER, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee

DONALD SVOBODA, Department of Pathology, University of Kansas Medical Center, Kansas City, Kansas

GEORGE W. TEEBOR, Department of Pathology, New York University School of Medicine, New York, New York

ARTHUR C. UPTON, Health Sciences Center, State University of New York at Stony Brook, Stony Brook, New York

FREDERICK URBACH, Temple University Health Sciences Center, Skin and Cancer Hospital, Philadelphia, Pennsylvania

J. H. WEISBURGER, Naylor Dana Institute for Disease Prevention, American Health Foundation, New York, New York

G. M. WILLIAMS, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania

Preface

This series of books attempts to present, in a comprehensive manner, the field of oncology divided into three major areas; etiology, biology, and therapy. These books should serve as landmarks in the rapidly expanding experimental and clinical "universe" of this field. To some, they will be introductory; to others, a summary; for all, critical comments on the future of research. In recognition of the difficulties inherent in attempting to pause and reflect while experimental data emerge with ever-increasing rapidity, the presentations take the form of *overviews* rather than *reviews*. Where possible, an historical perspective on observations and experimentation which led to our present understanding is presented, the state of the art in technique and approach is reviewed, and the gaps in knowledge and in technique are indicated. The aim throughout is integration—using the findings from one approach for comparison with others.

The tremendous expansion of interest in oncology as a medical-biological discipline stimulated the publication of these volumes. This expansion, well warranted in terms of the impact of oncology on human morbidity, has been characterized by at least three phenomena. First, there has been an enormous increase in money and manpower devoted to the investigation and treatment of malignancy. That the research has become more and more "directed" or program-oriented signals the interest of those beyond the scientific community in the management of the effort. Second, increasing numbers of students are entering the field of oncology as their major training program. Third, public awareness of these activities has increased greatly, marked positively by large-scale support and negatively by hurried release of findings.

Nonetheless, one major problem continues to diminish the immediate importance of the results of every experiment and casts a shadow of doubt on the relevance of every observation. That problem is *our inability to define the malignant cell.* A vast amount of information exists that describes what this cell *does* and—to a lesser extent—*how* it does what it does; but the *why* evades us. Until now the malignant cell has been defined only in comparison with its normal version. We temporize, using the excuse that it is similar to its normal progenitor. Ultimately, our understanding of the malignant cell will rest on our ability to define the benign cell, within the study of cell biology. Once we acquire that knowledge, the

pattern of phenotypic schizophrenia which is typical of malignancy may assume real meaning. Until we grasp its definition, we will be able to describe the malignant cell only in the most general way, as a cell whose sense of order is defective—a cell which has lost its sense of belonging to a larger community. One might suggest then that the malignant cell is one which attempts to break free from its metazoan community and return to the primeval condition of individuality.

The impact of basic research on oncology has been particularly impressive in the recent search for the etiology of malignancy. Equally impressive is the contribution of clinical observation. For over a century, the association between exposure to specific substances or participation in particular occupations and an exceptional incidence of specific forms of tumors has been recognized. The epidemiological approach remains as pertinent today as ever in studying etiology, whether it relates to the ingestion of "natural" substances in the instance of hepatocarcinogenic aflatoxin or to the suspected relationship of vinyl chloride and malignancy. It is therefore in the study of etiology that the dual disciplines of laboratory investigation and clinical observation best demonstrate a harmony of effort.

The search for the effects of carcinogenic agents cannot be separated from the search for the etiology of malignancy. Without an appreciation of the nature of malignant development, we are helpless to define the key macromolecular events induced by such agents. We cannot differentiate between obligatory alterations and the broad spectrum of unrelated effects produced by oncogens. The strategy is clear: (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.

The purpose of the first volume in this treatise is to present the progress that has been made toward these goals and to delineate the vast as yet unknown areas.

F.F.B.

New York

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