CHEMICAL CARCINOGENESIS AND CANCERS

Chemical Carcinogenesis and Cancers

By

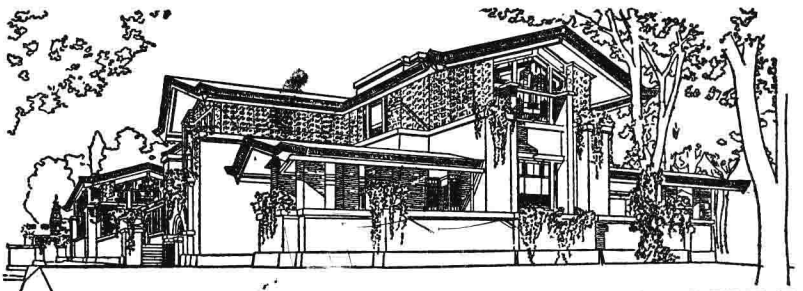
W. C. HUEPER, M.D.

Chief
Environmental Cancer Section
National Cancer Institute
Bethesda, Maryland

and

W. D. CONWAY, Ph.D.

Former Senior Chemist
Environmental Cancer Section
National Cancer Institute
Bethesda, Maryland



CHARLES C THOMAS • PUBLISHER
Springfield • Illinois • U.S.A.

Published and Distributed Throughout the World by
CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.
NATCHEZ PLANTATION HOUSE
735 North Atlantic Boulevard, Fort Lauderdale, Florida, U.S.A.

Library of Congress Catalog Card Number: 64-14058

With THOMAS BOOKS careful attention is given to all details of manufacturing and design. It is the Publisher's desire to present books that are satisfactory as to their physical qualities and artistic possibilities and appropriate for their particular use. THOMAS BOOKS will be true to those laws of quality that assure a good name and good will.

Printed in the United States of America
X 2

A REDEDICATION

THE PROBLEM of occupational neoplasia and numerous and various disease conditions which lead to it form a part of the problem of physical and mental national health on which depends, in the final analysis, the vital strength of a nation, its cultural and economic efficiency, and its existence as a self-respecting, independent, and valuable part in the community of nations. The care, preservation and improvement of the health of the people as a whole represents one of the noblest and most important tasks of every genuine and honest government. Only that people is adequately equipped and prepared to face the unavoidable changes of fortune occurring in the life of every nation, and is able to withstand these perils with a firm confidence in its power, with an unshakable belief in its vital right of existence, and with an unquestioning conviction of its moral obligation of survival, that is sound in body, intellect, and soul. The fundamental requirements for a healthful living, not merely for a small, selected, and socially privileged group, but for the entirety of its citizens, must be safeguarded by suitable laws adequately enforced.

From Hueper, W. C.: *Occupational Tumors and Allied Diseases*, Springfield, Thomas, 1942, p. 8-18.

FOREWORD

Our Living Chemistry Series was conceived by Editor and Publisher to advance the newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspective of human disorders.

Dr. Hueper and Dr. Conway of Bethesda organize and interpret the amassed thought on, and experience with, chemical carcinogens that have accumulated in this era. They not only unravel the biological phenomena in experimental carcinogenesis for cancer research, but the chemical mechanisms in human neoplasms for clinical appraisal. The work thus stimulates new insights into the chemical pathogenesis of neoplasia, delineates environmental carcinogenic hazards for preventive measures, and depicts occupational carcinogens for chemical control. The transformation of normal tissues into cancerous growths can be induced by stimulating substances originating within the organism or in the outer environment. Among the most specific are certain viruses, hormones, metazoic parasites; next in order are carcino-

genic substances; and last are the various radiations. Some 1500 compounds tested for carcinogenic activity yielded 400 carcinogens, but it is impossible to correlate chemical constitution with carcinogenic activity. Within a single group of compounds important foci of activity can be identified but different groups show extraordinary variations in composition, especially polycyclic aromatic hdyrocarbons, aromatic amines, chlorocompounds, mustards, ethyleneimines, steroids, propriolactone, tricycloquinozoline, and some inorganic substances.

Chemical compounds with totally unrelated structures produce neoplastic change. Aromatic carbons act at the site of application. Aromatic amines affect an organ remote from the site of entry into the body after metabolic conversion into a potent carcinogen and prompt detoxification with subsequent exposure to the bladder sufficient to produce carcinoma. Compounds of totally unrelated structures given orally may produce tumors of the liver, determined by the way in which the cell metabolizes the carcinogenic agent and the changes which occur in the cell during carcinogenesis. Liver carcinogens are the precursors of the active carcinogen and the tissue on which they act is that in which they are metabolized. Environmental carcinogens induce cancer at various sites—anthracene in the skin, crude mineral oil in the eyes, chromates in the respiratory system, benzol in the reticuloendothelial system, β-napthylamine in the urinary system.

The first environmental carcinogen, coal soot, was recognized as the cause of cancer two centuries ago, but the spectrum of potential agents has grown to mammoth proportions with the demonstration of carcinogens in food additives, drugs, cosmetics and consumer goods; in industrial plants, automobile exhaust and tobacco smoke; in radioactive matter dispersed in air, water and soil; and even in nutritional regimen. Biologic adaptation to naturally occurring environmental carcinogens, such as sunlight, ionizing radiation, chemicals and dyes, evolved throughout mankind's existence on earth via detoxification, chemoimmunity and pigmentation but natural protection against sudden onslaught of increasing numbers of macromolecular chemicals is questionable in a technological civilization advancing by scientific adventures involving calculated risks. The authors plead for concerted world

action against this medical opprobium by delimiting human exposure to chemical carcinogens with every possible means at our command by testing new drugs, insecticides, dyestuffs and chemicals for carcinogenic activity before release to the public. Who would not help a trifle to prevent what he would give a thousand worlds to cure? Pars sanitatis velle sanari fuit.

I. NEWTON KUGLEMASS, M.D., PH.D., SC.D., *Editor*

PREFACE

THE COMPLEX and increasingly important problems related to environmental carcinogens and cancers, particularly those created by the indiscriminate introduction of a growing number of man-made carcinogens into the human economy, have become during recent years the serious concern not only of public health agencies, medical and health professions, legislatures, courts, compensation commissions, the legal profession, labor organizations and managements of industries and of commercial establishments, but especially also of the general public. This rather recent development is mainly due to the fact that the rapidly accumulating information on this subject has definitely demonstrated the frequent spread of carcinogens and cancer hazards originally encountered only under occupational conditions, into the general human environment. Numerous chemical carcinogens of this type have been introduced during the past century, and especially during the last fifty years into many products of the general economy as ingredient or impurities of general consumer goods, such as food additives, food contaminants, drugs, cosmetics, economic poisons and household and sanitary goods, and have entered the human environment in the form of chemical pollutants of the air, water, and soil.

The growing awareness of large parts of the general public concerning the distinct risks to life and health associated with an undue and often needless and avoidable contact with such environmental carcinogens has been instrumental during the past decade in bringing about the enactment of several protective laws and regulations in various countries and local jurisdictions regarding the manufacture of such chemicals, their use or introduction into products required for daily living and their release as effluents into the atmosphere and into public bodies of water. The various provisions incorporated in these legal measures furnish at present only a limited amount of control of the actual and potential en-

vironmental cancer hazards. They have exerted nevertheless, even in their inadequate form, a considerable impact on the policies and practices of commercial concerns producing, processing, handling, packaging, shipping and merchandising carcinogenic chemicals and consumer goods containing such chemicals. In fact, the curtailment of the industrial production and of the commercial use of several known human carcinogens accomplished during the last decades in several countries either on a voluntary basis or by the enforcement of newly enacted laws, has amply demonstrated the appreciable financial risks to industry and commerce associated with such activities because of the potentially large scope of such cancer hazards to the general population and in view of their distinct significance to public health, legislation, national economy, international commerce, and sociology.

One of the most important aspects of this newly acquired knowledge on environmental carcinogens relates to the practical application of the available information to the many chemicals either synthesized in research laboratories or isolated from natural sources and intended for use in the human economy.

Industry faces to an ever increasing degree the need and obligation of testing such chemicals not only for acute and chronic toxic properties but of screening them also by suitable procedures for carcinogenic qualities. It is important that the usefulness of and the indications for individual test procedures appropriate for such purposes are not always satisfactorily established. The resulting methodologic uncertainties have hindered in the past the adoption and enforcement of standardized practices and policies as well as the fair and effective fulfillment of some of the newly enacted legal requirements by industry.

Legislatures and governmental agencies confronted with the task of formulating and enforcing laws and regulations intended for the proper protection of special worker groups, as well as of the general public, against cancer hazards created by the production, release and use of chemical carcinogens, are faced for the same reasons with corresponding difficulties. Their complex and important efforts directed at safeguarding the legitimate interests of the people against unnecessary and unwarranted exposures to these dangerous carcinogenic chemicals have been complicated at

times and have been interfered with in the past by the absence of a comprehensive and competent compilation and critical analysis of the factual scientific and practically applicable information already existing on this subject. The resulting uncertainty prevailing on some aspects of this problem has enabled at various occasions, some financially interested commercial parties and their scientific fellow travelers to advance allegations and to render testimony which confused and obscured the real issues involved, minimized and ridiculed the serious dangers to the general health created by chemical carcinogens, and belittled, and maliciously denounced the scientific competence and the character of those experts of environmental carcinogenesis defending without fear or favor, the public interest.

The availability of a comprehensive and judiciously prepared text in which the numerous and often isolated facts and observations on chemical carcinogens and carcinogenesis found widely scattered in the scientific literature, are compiled, coordinated and integrated, and in which the various biologic screening methods are described and evaluated for their significance, merits and special indications, doubtlessly represents a much needed and constructive approach for alleviating the presently disconcerting situation.

In this book an attempt is made to fill this gap to the extent made possible by the amount and type of information on hand. The treatise thus might serve as a source of reference to published data on chemical carcinogens and carcinogenesis as well as a guide to all those engaged in developmental chemical research and in the performance and interpretation of carcinogenic bioassays of chemicals. It may profitably also be consulted by members of legislatures, law enforcement agencies and public health departments interested in and charged with the proper protection of the general population as well as of special worker groups against health hazards from contact with chemical carcinogens.

Because of the many remaining defects in the existing knowledge on chemical carcinogens and carcinogenesis which involve in part fundamental aspects of the problem of cancer, some of the conclusions reached had to remain of provisional nature and represent the best that could be obtained at the pre-

vailing circumstances. In such instances the information supplied provides directives and directions valuable for future research since the critical assessments made define the limitations which apply to the interpretations of the data evaluated. The evidence presented and interpretations arrived at should be useful, moreover, in the formulation of sound policies and practices for inaugurating a comprehensive program of preventive control of cancer hazards caused by exposures to chemical carcinogens. The concluding chapter, therefore, discusses the justification for and type of measures needed for achieving the important goal of securing adequate protection of the health of the general population living in a chemicalized man-made environment.

No attempt has been made to supply a complete or comprehensive list of literature references because such a compilation would have added unduly to the size of the book and to its publication expenses. The references included provide, however, an adequate documentation of the subject matter discussed and of the interpretations made.

ACKNOWLEDGMENT

OUR SPECIAL gratitude goes to Mrs. N. Cooper who untiringly managed the preparation of the manuscript through its sometimes difficult phases.

Our thanks are also due to Mrs. W. D. Conway for valuable assistance in the preparation of some parts of the manuscript.

W. C. HUEPER
W. D. CONWAY

Bethesda, Md.

CONTENTS

CHEMICAL CARCINOGENESIS AND CANCERS