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Index
Session 1: Hydrocarbon Carcinogenesis

Berenblum, I. (Rehovoth): A Re-evaluation of the Concept of Cocarcinogenesis
Van Duuren, B.L. (New York, N.Y.): Tumor-promoting Agents in Two-stage Carcinogenesis
Homburger, F. and Treger, A. (Cambridge, Mass.): Modifiers of Carcinogenesis

Session 2: Carcinogenesis Viewed as Function of Agent

Bryson, George and Bischoff, Fritz (Santa Barbara, Cal.): The Limitations of Safety Testing
Wogan, G.N. (Cambridge, Mass.): Naturally Occurring Carcinogens in Foods
Eckardt, R.E. (Linden, N.J.): The Role of Experimental Biology and Toxicology in Rendering the Human Environment Safe (After-dinner Speech)

Session 3: Carcinogenesis Viewed as Function of Target

Boyland, E. (London): The Correlation of Experimental Carcinogenesis and Cancer in Man
Dao, T.L. (Buffalo, N.Y.): Studies on Mechanism of Carcinogenesis in the Mammary Gland
Deckers, C. (Louvain): Immunological Aspects of Carcinogenesis
Miller, James A. and Miller, Elizabeth C. (Madison, Wis.): The Metabolic Activation of Carcinogenic Aromatic Amines and Amides
Saffiotti, U. (Chicago, 111.): Experimental Respiratory Tract Carcinogenesis

Session 4: Test Methods and Relation to Man

Della Porta, G. and Terracini, B. (Milan): Chemical Carcinogenesis in
Infant Animals 334

IV Index

Burdette, W. J. (Houston, Tex.): Causality, Casuistry and Clinical Carcinogenesis 395
Mantel, N. (Bethesda, Md.): Some Statistical Viewpoints in the Study of Carcinogenesis 431
Poel, J.W.E. (Pittsburgh, Pa.): Bioassays with Inbred Mice: Their Relevance for the Random-bred Animal 444

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This volume is dedicated to
the retiring Director of the National Institutes of
Health, United States Public Health Service,

JAMES A. SHANNON

whose courageous championship of basic
biomedical research made possible much of the
progress reported in this series.

Editor's Foreword

This volume contains most of the papers read at the International
Symposium on Carcinogenesis and Carcinogen Testing organized by BioResearch
Institute, Inc., Cambridge, Massachusetts, at the Museum
of Science in Boston on November 8th and 9th, 1967.
Profound gratitude is expressed to the following sponsors who,
through their financial support, made this Symposium possible:

American Petroleum Institute
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During four half-day sessions, luncheon meetings and a banquet,
twenty-five papers were presented, grouped under the headings of
Hydrocarbon Carcinogenesis, Carcinogenesis Viewed as Function of Agent,
Carcinogenesis Viewed as Function of Target, and Test Methods and
Relation to Man.
There were more than two hundred participants from most of
the United States and from Canada, the United Kingdom, Belgium,
Italy, Israel, Japan and Switzerland.
The purposes of this symposium were to review the past history
of carcinogenesis, to define various concepts in the fields of carcinogenesis
and cocarcinogenesis, to evaluate the current state of the
art as applied to the study of initiators, co-factors and the behavior
of induced tumors, to project progress into the future, and to
evaluate the practical significance of some of the observations made
on carcinogenesis in animal experiments.
Shimkin and Triolo reviewed the landmarks of progress in cancer research, from which they drew conclusions for future research planning, especially emphasizing the historically proven productivity of multidisciplinary cooperation.

Both Boyland and Burdette suggested, after their reviews of some of the past achievements of carcinogenesis research, that study of the less common tumors of man in relatively small groups of individuals now deserves major emphasis.

Editor's Foreword IX

Most of the studies presented at the Symposium, however, dealt with results obtained through animal experiments. Weisburger (to appear in a future volume of this series) discussed hepatic carcinogenesis as a field wherein epidemiological studies on the geographical clustering of human liver cancer may be related to the known modifying factors of experimental hepatic carcinogenesis in animals. In hepatoma induction in animals, metabolic activation of the chemical carcinogen affecting the liver is required and occurs through biochemical conversion to active intermediates. Miller and Miller discussed N-hydroxylation as one metabolic process that leads, in the rat, to more carcinogenic derivatives in the case of 2-acetylaminofluorene and other aromatic amines and amides. Esters of the N-hydroxy derivatives are stronger carcinogens than the N-hydroxy compounds themselves, and their ready reaction in vitro and in vivo with methionine, guanosine and with other amino acids has been demonstrated. This suggests a two-step metabolic activation of many carcinogenic aromatic amines and amides through N-hydroxylation and esterification.

Deckers discussed immunological factors in rat hepatocarcinogenesis and showed how pretreatment with microsomal fractions from hepatomas during the latent period of 2-acetylaminofluorene carcinogenesis can increase the latent period and lower the tumor yield. Heidelberger (who elected not to commit his remarks to paper) discussed the possible mechanisms of hydrocarbon carcinogenesis and concluded that it is probably necessary for hydrocarbons to be metabolized by the cells before binding to proteins and nucleic acids can occur. To study whether hydrocarbons cause cancer by direct transformation, selection of pre-existing cancer cells or activation of latent viruses, an in vitro system derived from mouse prostate cells was developed wherein direct in vitro carcinogenesis through hydrocarbons appears to have been achieved and spontaneous
transformation has not been observed. Quantitative studies of hydrocarbon carcinogenesis of these mouse cells in vitro are thus now possible. Diamond discussed the role of polycyclic hydrocarbons in in vitro monolayer cultures of rodent cells, which differ in their response from primate cells. The response of resistant and sensitive cells appeared to be related to the amounts of hydrocarbon that become firmly bound to cellular protein and nucleic acids.

Other forms of hydrocarbon carcinogenesis discussed were the induction of respiratory tract neoplasms in hamsters by the intra-tracheal administration of polycyclic hydrocarbons in various forms (Saffiotti), and the induction of breast cancer in rats by the feeding of polycyclics (Dao). In the latter study, the effect of polynuclear aromatic hydrocarbons on the rat mammary gland RNA metabolism was shown to be hormone-dependent.

Coombs and Croft reported on some twenty carcinogenic hydrocarbons and ketone derivatives of cyclopenta[a]phenanthrene. Cancers were produced with these compounds in skin and/or subcutaneous tissue of mice, and a general reappraisal of the role of steroids as potential precursors of endogenous carcinogenesis is now desirable.

Southam reported recent studies on the interaction of various non-oncogenic viruses with methylcholanthrene and other carcinogenic agents. The increased oncogenic response of mouse skin to hydrocarbons brought about by non-oncogenic viruses offers a possible explanation for the variability of tumor incidence in human populations exposed to carcinogens.

The effects of pretreatment of mice exposed to subcutaneous injections of benzo[rst]pentaphene (dibenzpyrene) with oxidative derivatives of the carcinogen (acetoxy, benzoate, quinone) were discussed by Homburger, among other modifiers of carcinogenesis. These oxidative derivatives, as well as partially reduced derivatives of various polycyclic hydrocarbons, play an important role in the assay of carcinogenic potency of complex mixtures such as smoke, exhaust fumes, etc.

The concept of cocarcinogenesis was greatly clarified by Berenblum, who defined seven distinct types of cocarcinogenesis and defined their possible role in human cancer.
Van Duuren discussed the isolation and structure determination of the active principles of croton oil, especially its phorbol esters, and demonstrated how the use of these chemically known substances can contribute to the quantitative knowledge of the mechanism of cocarcinogenesis.

A number of more recently discovered or restudied carcinogens were discussed by Boyland, including cadmium and bracken (Pteris aquilina); asbestos, nickel, chromates and other metals by Furst and Haro (to be published in a later volume of this series), and silica dusts and diatomaceous earth by Bryson and Bischoff, who pointed out the limitations imposed by solid state carcinogenesis upon subcutaneous carcinogen testing.

Editor’s Foreword XI

Wogan discussed carcinogens introduced into food from spoilage fungi such as aflatoxins (Aspergillus flavus), products from Pennolium islandicum and foodstuffs with carcinogenic activity such as cycasin, pyrolizidine alkaloids and components of bracken fern.

Carcinogen testing was viewed from the statistician’s angle by Mantel, and its complexity in the case of tobacco-smoke carcinogenicity was reviewed by Wynder and Hoffmann.

Della Porta demonstrated the high sensitivity of infant mice toward DMBA, methylcholanthrene and nitrosomethylurea, and stressed the potential usefulness of the newborn or infant mouse for carcinogen testing. Poel observed variations in long-term cocarcinogen and carcinogen testing in the responses of inbred strains of mice and suggested that random-bred hybrids might be better subjects for such tests.

Homburger reviewed the many procedures suggested in the literature for accelerated carcinogen testing and showed that the time of latency in subcutaneous carcinogenesis in mice with benzo[rst]pentaphene can be halved by transfer of pooled carcinogen injection sites from several animals into one secondary host. Malignant in vivo transformation of subcutaneous fibroblasts in Syrian hamsters requires only days as compared to weeks in mice, and a greatly shortened carcinogen test in hamsters is a distinct possibility.

The present status of a current National Cancer Institute survey of needs in the area of chemical carcinogenesis was reviewed by Cantarow (unpublished remarks), and the role of government in maintaining a healthy environment was the subject of a banquet address by Elliot L. Richardson, Attorney General of Massachusetts.
and former Assistant Secretary of the Department of Health, Education and Welfare (unpublished remarks), while the role of industry in this respect was discussed by Dr. Robert E. Eckardt. The editor expresses his appreciation to all the Symposium participants for the care and diligence that went into the preparation of their contributions and for their punctuality in submitting their manuscripts. He also acknowledges with gratitude the publisher’s gift of the invitations, programs and registration forms, and Mrs. Mary Miller’s editorial assistance.

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Editor
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