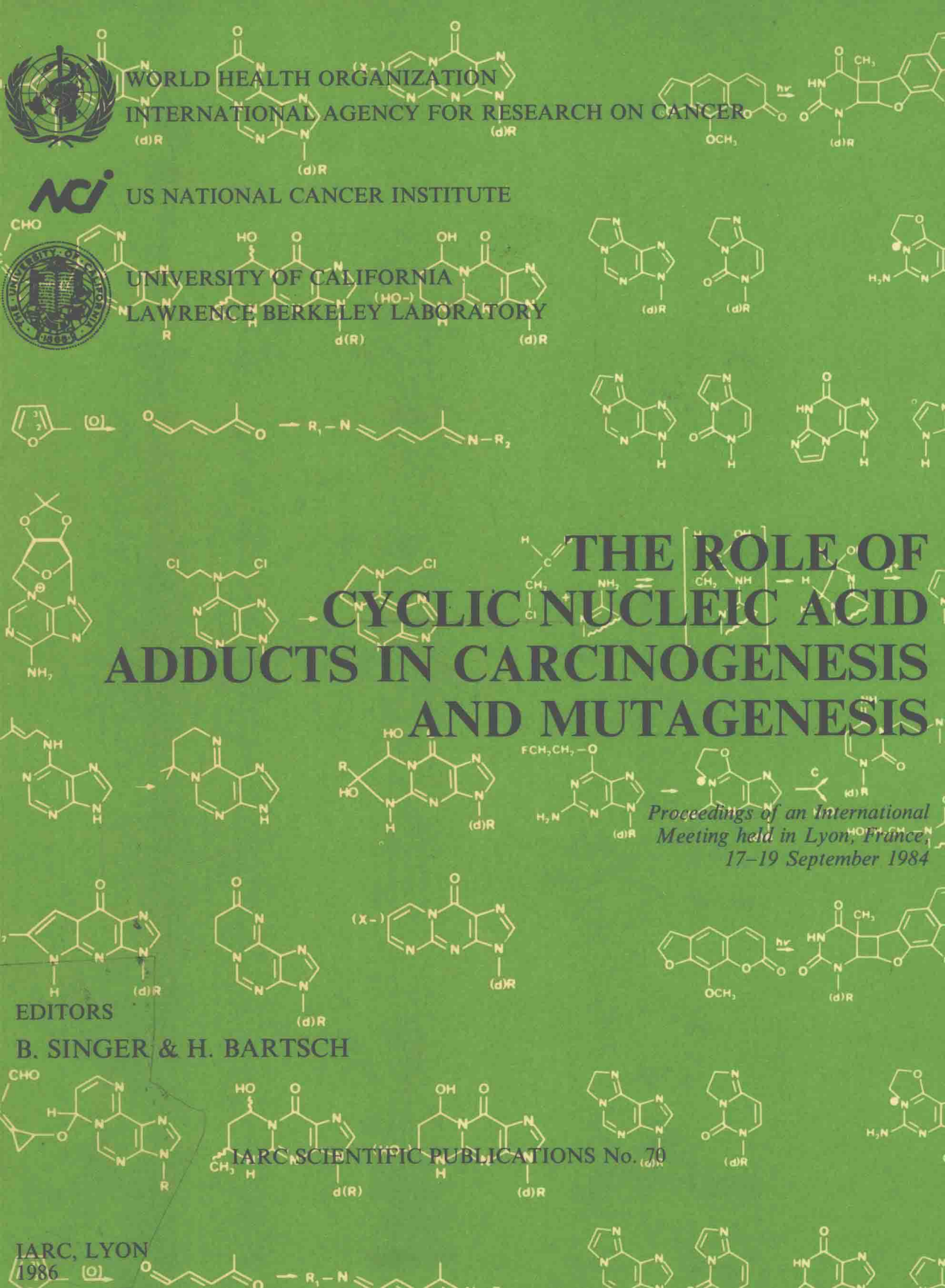

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

US NATIONAL CANCER INSTITUTE

UNIVERSITY OF CALIFORNIA
LAWRENCE BERKELEY LABORATORY

THE ROLE OF CYCLIC NUCLEIC ACID ADDUCTS IN CARCINOGENESIS AND MUTAGENESIS

Proceedings of an International Meeting held in Lyon, France, 17–19 September 1984

EDITORS
B. SINGER & H. BARTSCH

IARC SCIENTIFIC PUBLICATIONS No. 70

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The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently financed organization within the framework of the World Health Organization. The headquarters of the agency are at Lyon, France.

The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon, and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency are intended to contribute to the dissemination of authoritative information on different aspects of cancer research.

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FOREWORD

It is now commonly agreed that modification of DNA by chemical carcinogens is a critical step in the initiation of many neoplasias in experimental animals, and probably also in humans. Chemotherapy of human cancers using antineoplastic agents, many of which exert carcinogenic side effects, is also believed to involve a DNA modification that is related to their cytotoxic action. Because of the fundamental role of DNA interactions, research over the past three decades has been directed to the characterization and study of the consequences of the macromolecular adducts produced by a variety of known carcinogens in human and animal cells. During the past decade, increasing interest has been directed to a number of carcinogenic and mutagenic agents that share the common property of being able to react with nucleic acid bases to form one or more additional ring systems, i.e., exocyclic DNA base adducts. Although the structure and formation of such adducts with industrial carcinogens, chemotherapeutic agents and products formed by metabolic processes, like bifunctional aldehydes, have been reported increasingly, only the multidisciplinary group gathered at this conference has addressed the question of whether the cyclic adducts have any biological relevance. At this meeting, common areas of, as well as gaps in, knowledge in this field were identified, and it became clear that further chemical, biochemical and immunological studies are needed to assess how this group of widely distributed compounds produces cancer.

This volume comprises the proceedings of a meeting held at IARC in Lyon in September 1984. It appears to be the first comprehensive overview on cyclic adducts formed from a variety of compounds, and includes sections on occurrence, epidemiology, carcinogenic effects, metabolism and sensitive methods for detection.

Unlike most conference proceedings, the papers in this volume underwent peer review. The IARC would like to thank the following for reviewing critically the contents of the papers: M.K. Conner, F.P. Guengerich, N.J. Leonard, J.W. Lown, R. Shapiro, B.S. Strauss and J.A. Swenberg.

I should like to thank B. Singer, Laboratory of Chemical Biodynamics, University of California, Berkeley, California, one of the co-organizers, and the National Cancer Institute, NIH, Bethesda, Maryland, for co-sponsoring this meeting.

L. Tomatis, M.D.
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INTRODUCTION

There are a substantial number of human and animal carcinogens, widely used in industry, chemotherapy, or formed by metabolic processes or combustion, which have in common the ability to form cyclic nucleic acid derivatives. These include vinyl halides, alkyl carbamates, bifunctional aldehydes, 2-haloalkylnitrosamines and cyclic nitrosamines, acrylonitrile, etc., all of which, or their metabolites, react with exocyclic amino groups, particularly that of guanine.

Progress in understanding how these chemicals exert their biological effects has been impeded by the perception of a lack of a critical mass of scientists and of data. This situation, in reality, no longer exists as shown by this meeting. However, prior to this conference there was no unifying focal point. Chemists studied a single type of chemical reaction for its own sake, while biologists tested another array of compounds for mutagenicity, and metabolic pathways were investigated by other scientists, but the products were not necessarily related to those studied by chemists or biologists. It could be said that tunnel vision impeded elucidation of the general problem.

As a result of this multidisciplinary conference, some common areas of knowledge and of concern were identified. Although cyclic $1,N^2$-guanine derivatives were readily identified *in vitro*, there is little evidence for their occurrence in DNA *in vivo*, but some evidence in RNA. Thus RNA adducts should also be studied *in vivo*. There are, in addition to the one type of guanine cyclic adduct, a multiplicity of minor adducts found *in vitro*. These should also be identified, and ultrasensitive methods for detection of all such derivatives *in vivo* need to be developed. Most of the chemicals discussed also form cross-links as a result of their bifunctional character, and the biological role of such cross-links needs further investigation. It also became apparent that repair has not been demonstrated unequivocally for any cyclic adduct. Finally, the carcinogenicity of most mutagenic aldehydes has not been established, due either to a lack of testing or to poor testing.

It is now clear that future chemical, biochemical and enzymological studies are needed to assess whether and how this group of widely distributed chemicals affect human health.

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