WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

CHEMICAL CARCINOGENESIS ESSAYS

Editors:

R. MONTESANO
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W. DAVIS

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Proceedings of a Workshop on Approaches to Assess the Significance of Experimental Chemical Carcinogenesis Data for Man organized by IARC and the Catholic University of Louvain, Brussels, Belgium 10-12 December 1973

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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, and it has Research Centres in Iran, Kenya and Singapore.

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

A significant portion of the programme of the International Agency for Research on Cancer is directed to the identification of those chemical substances in the environment which present a carcinogenic hazard for man. This programme is developed along two major lines. On the one side, epidemiological studies have been developed, directed to finding carcinogens already in the environment. On the other side, research is directed to the development of better laboratory techniques aimed at forecasting the carcinogenic effect of the many thousands of chemicals to which man is exposed in modern society.

Accordingly, the Agency was delighted to accept the invitation to organize a joint meeting with the Catholic University of Louvain in Brussels to explore current problems in chemical carcinogenicity testing, with special reference to better laboratory technology. We are most grateful for the substantial support we received from the Belgian government and to Professor S. Halter, Secretary-General of the Ministry of Public Health and the Family, and Dr F.J.C. Bosquet, Director-General for Social Medicine of the same ministry. We were very happy when Professor Z.M. Bacq, of the State University at Liège and a member of our Scientific Council, agreed to be Honorary President of the meeting.

The meeting was a success, and I wish to express my thanks to Professor Dumont, Professor Maldague, Dr Tomatis and Dr Montesano, who put in an immense amount of work to prepare it. Finally, I want to thank also all the contributors whose work appears in this volume.

John HIGGINSON, M.D.

Director

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INTRODUCTION

Since Yamagiwa and Ichigawa in 1915 first produced tumours on the skin of rabbits by painting them with coal-tar, thousands of substances have been tested for carcinogenicity on a wide variety of experimental animals by painting, injecting or feeding. Some of these tests were positive, many substances producing tumours in several different species. Even so, it has never been possible to conclude with complete certainty that a substance found to be carcinogenic in animal tests would of necessity be carcinogenic for man. The most that could be said was that it would be better to avoid exposure to substances that were obviously carcinogenic to several animal species.

However, the current problem is that modern industrial and agricultural societies are exposing ever-increasing populations to a very wide variety of chemical substances in response to the pressure for higher living standards in both developed and developing countries. Many of these, such as pesticides, insecticides, fertilizers, petroleum products, plastics precursors, building materials, pharmaceutical products, are essential components of 20th century civilization. To remove unnecessarily such a substance from the human environment might produce severe damage to society. Governments, therefore, through their public health authorities, need to be very precisely informed of the level of risk represented by a given chemical in the environment.

Short of the formal proof of an epidemiological study, we need to be able to set up experimental models that will allow us to approach more closely to being able to extrapolate from animal tests to man. However, some recent epidemiological findings have shown that earlier experimental carcinogenesis data could well have predicted a carcinogenic effect of a chemical in man. For stilboestrol, bis(chloromethyl)ether and vinyl chloride, the evidence of carcinogenicity in experimental animals existed from 4 to 20 years before case reports or epidemiological studies demonstrated their carcinogenicity in man. It is reasonably certain that other examples of this type will become apparent in the future, but without objective criteria for extrapolating experimental carcinogenesis data to man there is no way of making any reliable predictions.

It was with the aim of developing such criteria to permit a better assessment of the significance of experimental carcinogenesis data for man that a workshop was convened jointly by IARC and the Catholic University of of Louvain in Brussels from 10 to 12 December 1973. This volume contains the papers presented there and the discussion that each provoked.

We were fortunate in that so many of the invited scientists who are specialists in this field were able to contribute to this book, which we

believe will serve as a definitive review of the current state of the art and as a guide to the road for future development.

We are extremely grateful to Professor P. Dumont and Professor P. Maldague and their excellent staff, on whose strenuous efforts and organizational capacity much of the success of the meeting depended. We appreciated very much being guests of a school which created the best possible atmosphere for the meeting and we should like to thank Professor Magee who, as an excellent chairman, also contributed much to the congenial atmosphere.

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CARCINOGEN METABOLISM IN EXPERIMENTAL ANIMALS AND MAN

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How accurately do the results of studies with a chemical carcinogen in an animal or in a cell culture system predict the toxicity of the chemical in man? This is an important question, since the human population is exposed to numerous chemicals, both man-made and of natural occurrence, that are carcinogenic in animals or which cause mutations and malignant transformations in cultured cells. Although studies presented at this workshop have pointed out the difficulties in knowing with certainty whether a chemical which causes cancer in an experimental animal is carcinogenic in man, it is likely that as our knowledge expands we shall be able to extrapolate the results of animal data to man with greater certainty than we can at the present time. We would like to discuss some metabolic considerations that may provide a means of better extrapolating to man the results of carcinogenesis studies in animals.

SPECIES DIFFERENCES IN THE METABOLISM OF DRUGS AND CARCINOGENS

Since foreign chemicals are metabolized at widely different rates in different animal species (i.e., one species may metabolize a chemical 10 to 20 times more rapidly than another species), it is difficult to use the dose of the substance as a basis for the extrapolation of animal data from one species to another and from animals to man. The marked species differences that occur in the metabolic half-life of hexobarbital, antipyrine and aniline are shown in Table 1. It should be noted that a characteristic species difference occurs for the metabolism of each drug. Although the mouse metabolizes hexobarbital and antipyrine severalfold more rapidly than the rabbit, these two species metabolize aniline at the same rate.

A marked species difference exists in the dose of ICI 33,828 (Fig. 1) needed to exert a pharmacological effect on the pituitary gland. Although a 200-fold difference was observed in the dose of ICI 33,828 needed to inhibit the elaboration of pituitary gonadotrophin in various species, the blood concentration associated with the pharmacological action of the drug was about the same in all species (Duncan, 1963). The rabbit, dog and man