CIBA FOUNDATION SYMPOSIUM

ON

CARCINOGENESIS

Mechanisms of Action

Editors for the Ciba Foundation

G. E. W. WOLSTENHOLME, *O.B.E.*, M.A., M.B., B.Ch.

and

MAEVE O'CONNOR, B.A.

With 48 Illustrations

This volume is respectfully dedicated by the Chairman and members of the Symposium to the memory of the late

SIR ERNEST KENNAWAY,
D.M., D.SC., F.R.C.P., F.R.S.
1881–1958

Printed in Great Britain

CARCINOGENESIS

Mechanisms of Action

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Under the guidance of its distinguished Trustees, the Foundation offers accommodation to scientists from all over the world at its home in Portland Place. Foremost in its activities is the organization of small conferences, the proceedings of which are published in book form in the manner of the present volume. The Foundation convenes many other informal discussions between research workers of different disciplines and different nationalities and each year invites an outstanding authority to deliver a special lecture. An exchange programme between French and British postgraduates is conducted and a library service is available. Furthermore, the Ciba Foundation attempts in every other way possible to aid scientists, whether they be Nobel Laureates or young graduates making their first original contribution to research.

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PREFACE

After the VIth International Cancer Congress in Brazil in 1954, the Director of the Ciba Foundation was approached with a suggestion that immediately before the VIIth Congress in London in 1958, a symposium on carcinogenesis might be held at the Foundation. The Director readily agreed to this proposal. The organization of the symposium was undertaken by the Deputy Director, who was greatly helped by the constant and invaluable advice of Professor A. Haddow, F.R.S., and Professor E. Boyland.

The conference was designed on established Ciba Foundation lines and Professor Haddow, who acted as Chairman on this occasion, directed its course with the lightest but surest of touches. The individual members of the group represented different disciplines and countries, but all were actively engaged in some aspect of cancer research. A sad loss to the meeting was the death of Sir Ernest Kennaway on January 1st, 1958, which robbed the symposium of one who would have been a most valuable contributor.

When the programme was drawn up ample time was allowed for informal discussion of the papers offered. Such thorough discussion, which is a feature of these symposia, is only made possible by limiting the number of those taking part. The editors therefore hope that the complete record of the proceedings which is presented here will afford the pleasure of vicarious participation to all those working on cancer research who could not be invited to attend this meeting.

List of those participating in or attending the Symposium on "Carcinogenesis: Mechanisms of Action", 24th–26th June, 1958.

P. Alexander	Chester Beatty Research Institute, London
I. Berenblum	Dept. of Experimental Biology, Weizmann Institute of Science, Rehovoth, Israel
F. Bielschowsky	Cancer Research Dept., University of Otago, Dunedin
Georgiana Bonser	Dept. of Experimental Pathology and Cancer Research, University of Leeds
E. Boyland	Dept. of Biochemistry, Chester Beatty Research Institute, London
A. Brues	Argonne National Laboratory, Lemont, Illinois
Sir Macfarlane Burnet	Walter and Eliza Hall Institute of Medical Research, Melbourne
H. Druckrey	Chirurgische Universitäts-Klinik, Freiburg im Breisgau
J. Furth	Children's Cancer Research Foundation, Boston, Massachusetts
H. N. Green	Dept. of Experimental Pathology and Cancer Research, University of Leeds
C. Hackmann	Inst. of Experimental Pathology, Farbenfabriken Bayer A. G., Wuppertal-Elberfeld
A. Haddow	Chester Beatty Research Institute, London
C. Heidelberger	McArdle Memorial Laboratory, University of Wisconsin, Madison, Wisconsin
I. Hieger	Chester Beatty Research Institute, London
E. S. Horning	Dept. of Experimental Pathology, Chester Beatty Research Institute, London
H. S. Kaplan	Dept. of Radiology, University of Stanford, San Francisco, California
V. R. Khanolkar	Indian Cancer Research Centre, Tata Memorial Hospital, Bombay
P. C. Koller	Dept. of Cytogenetics, Chester Beatty Research Institute, London
R. Latarjet	Laboratoire Pasteur de l'Institut du Radium, Paris
P. Loustalot	CIBA Ltd., Basle
R. H. Mole	Radiobiological Research Unit, Harwell
O. Mühlbock	Nederlandsch Kankerinstituut, Antoni van Leeuwenhoek-huis, Amsterdam
H. P. Rusch	McArdle Memorial Laboratory, University of Wisconsin, Madison, Wisconsin

M. H. SALAMAN	Dept. of Cancer Research, London Hospital Medical College, London
L. SEVERI	Division of Cancer Research, Istituto di Anatomia e Istologia Patologica, Perugia
R. TRUHAUT	Institut Gustave-Roussy, Villejuif, Seine
A. C. UPTON	Biology Division, Oak Ridge National Laboratory, Tennessee
A. L. WALPOLE	Pharmaceuticals Division, I.C.I. Ltd., Macclesfield, Cheshire
E. C. W. WEILER	Division of Biology, California Institute of Technology, Pasadena; and Max-Planck-Inst. für Virusforschung, Tübingen

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CHAIRMAN'S OPENING REMARKS

A. HADDOW

THIS symposium was arranged in relation to the VIIth International Cancer Congress, to provide an opportunity, in these very agreeable surroundings, for more detailed discussion than might be possible during the Congress itself. When the symposium was originally planned we obviously had hoped and expected that Sir Ernest Kennaway would be with us. In fact he had accepted, but it was not to be. In this audience, there is no need for me to say what his loss has meant. No-one had made a vaster contribution to this subject. In tribute, some of us had the thought that we might inscribe these proceedings, when published, to him.

The second paper this morning is on the Oppenheimer effect and here again we have had a very sad loss in Dr. Oppenheimer's death a couple of weeks ago. I do not know how many here knew him personally. He was a New York physician, always tremendously interested and active in research, but mostly in his own subject of cardiology. As you know, some years ago—comparatively late in his life—he made the discovery to which the second paper refers. While he was studying the production of hypertension in the rat, investing the kidney with cellophan to induce it, and keeping these animals for long periods of time, he unexpectedly noted the development of sarcomata in relation to the cellophan sheets. The observation has been very widely confirmed, and gave Dr. Oppenheimer (and Mrs. Oppenheimer, his helper) great delight, coming as it did towards the end of his career. That delight has certainly been shared by a great many people who through it became his friends.

In the '20s and '30s I think it is true to say that our subject was in the stage of the discovery and identification of carcinogenic agents. In the late '40s and in the '50s there took place

a marked shift of emphasis from the agents themselves towards the question of their mechanism of action. As far as we can see, there is no fundamental reason why we should not ultimately be able to decipher the process in chemical terms. As a corollary, we would then know the precise biochemical nature of the differences between normal and malignant cells, with all its implications for the control of cell division. Things are very different from the early '20s, in that we now have a tremendous range and variety of carcinogenic agents. These are so varied that their initial routes of action must inevitably be different—hence the title of this symposium, the *mechanisms* of action. Nevertheless the question is still quite open, whether malignancy may depend upon some key biochemical lesion or loss—about that we will be hearing something from Dr. Weiler later in the proceedings.

I think most of you will have seen the *British Medical Bulletin* for May of this year, devoted to the causation of cancer. This succeeds a similar issue in 1947, and there is a good deal to be learned in comparing the present issue with that of 11 years ago. We can never be satisfied or complacent, but there is certain evidence of a move towards greater precision in our knowledge now as compared with then, and there are many parts of the subject which are entirely new—for example, the carcinogenic action of many alkylating agents and their mechanism. It is of interest that even since this recent issue was completed, several developments have taken place which are altogether new. One I particularly have in mind is a sudden great increase in interest in the carcinogenicity of metals, and in the rôle of metals in carcinogenesis, about which I should like to say something further, later in our proceedings.

[The Chairman then made reference to the fact that during the course of the meeting Sir Macfarlane Burnet would go to Buckingham Palace, where the award of the Order of Merit would be personally bestowed upon him by Her Majesty the Queen.]

THEORIES OF CARCINOGENESIS

I. HIEGER

Chester Beatty Research Institute, Royal Cancer Hospital, London

THERE are at least two ways of interpreting carcinogenesis: first, that there is a limit to the functional integrity of the cells of long-life in the sense of an interval which is a substantial fraction of the lifespan of the body as a whole, after which the organizing capacity diminishes; or alternatively that some factor generated internally or introduced from the outside acts as a triggering device for the carcinogenic process. So far, our knowledge of carcinogenesis refers exclusively to the second case, and I shall confine myself therefore to carcinogens of three kinds, chemical, viral and environmental.

But before leaving the possibility of carcinogenesis without a carcinogen, one might ask whether senescence is conceivable without a gerontogen, or differentiation without a differentiator? The organizers are not much heard of nowadays—did someone find that a much simpler agent could be as effective as the sterol fraction of the dorsal lip of the blastopore?

Since carcinogens of completely different character exist, it follows that they are certainly not the ultimate stage in the chain of events between their application and neoplasia, and the gaps in our understanding, or, might I say, the missing links, are as elusive as the steps in any other drug action.

The problem of carcinogenesis has been faced—it is really too early to call it attacked—by an arsenal of scientific concepts, such as quantum mechanics, electronic characteristics of chemical molecules, and mutation of a biochemical, subcellular or cellular kind according to which level of organization is being considered.

Physicists and chemists having come to the aid of cancer research have naturally tried to find correlations between the

potencies of chemical carcinogens and their physicochemical properties such as the electronic configuration of the molecule, excess charge on the K region and the reactivity to osmium tetroxide. A table showing values for the two properties side by side does suggest an approximate agreement between biological and physicochemical order, and of course "order" is the operative word here.

In my opinion, the awkward inconsistencies which occur, the very small margins of physical characteristics which sometimes separate powerful and weak carcinogens, and the failure of the exponents to predict on physical grounds what compounds should or should not be carcinogenic, let alone the prediction of the structure of a "super carcinogen", make it difficult to believe that electronic theory has yet very much to offer as an explanation of the mechanism of carcinogenesis.

To begin with, the electronic characteristics are described by a number calculated to the second or third place of decimals, that is, defined to one part in 100 or 1,000. But the order in which the potencies can be arranged is quite a different matter. An experimental pathologist would consider himself lucky if he could reproduce his results to within 25 or 50 per cent, which is not good enough for the order of arrangement. Except for a few carcinogens there is no completely satisfactory way of comparing their potencies, and most workers would consider becoming involved in such studies as unrewarding. At the risk of telling my audience what they already know too well, might I point out that in attempting to arrive at an estimate of the relative potencies of carcinogens it is quite mistaken to employ doses larger than optimal ones or to place much reliance on crude average latent periods—the sensitive part of the curve relating dose and response should be used; skin does not react the same as the other tissues; species and strains and groups of animals have different sensitivities, even siblings of the same group of the same pure strain of mouse respond with different degrees of susceptibility. Tumour induction assays are often reproducible only by a factor of 2 or 5; that is to say that if a preparation of carcino-