



# CHEMICAL INDUCTION OF CANCER

By

GEORGE WOLF, B.Sc., D.Phil.

Assistant Professor, University of Illinois

Formerly Research Fellow, McArdle Memorial Laboratory,  
University of Wisconsin, and Harvard University ; and  
Research Associate at The Chester Beatty Research Institute,  
The Royal Cancer Hospital, London



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## FOREWORD

ALL who are actively engaged upon the experimental study of cancer, and especially upon the elucidation of its chemical causation, are well aware of a strong demand for some comprehensive, authoritative, yet not over-elaborate description of developments in this field, which would be of value at once to the general medical and scientific reader and to the interested layman. It is a matter for regret that the very pace of discovery has hindered the satisfaction of this need, by leading too many of us, in the excitement of the chase, to neglect our duty of more general exposition. Not only those to whom this book is primarily addressed, but his immediate colleagues in the field of cancer research also, are accordingly under a special debt to Dr. Wolf for providing, in short compass and eminently readable form, this unified and lucid account. That he is well qualified to do so is shown by his own contributions, made both in this country and in the United States.

A great part of the relevant work carried out in the past thirty years has been concerned with the discovery of chemical agents, both naturally occurring and purely synthetic, having the capacity to induce cancer under experimental conditions. Dr. Wolf has done ample justice to this important field, as also to the related problems of chemical constitution and biological action. At the same time his book reflects the change of emphasis of the past few years, as a result of which much more attention is being devoted to mechanisms of action, for example through studies of the chemical reactivity and metabolic fate of carcinogens, the contributions of the French school,

and the discovery and significance of carcinogenic activity in many nitrogen mustards and other biological alkylating agents. All these advances are now leading to very greatly increased confidence that the elucidation of the carcinogenic process will in fact lead, as had been hoped, to the means of its chemical or enzymatic control. Dr. Wolf's book therefore appears at an appropriate moment in the development of the subject, and is warmly to be commended as an admirable summary of the main experimental facts, for its balanced interpretation, and as a source not only of information but of stimulus as well. It will perhaps be specially welcomed by those wishing to acquaint themselves, without too great difficulty, with a field of research which, if it has of necessity developed along highly specialized lines, is nevertheless of the utmost importance towards the ultimate solution of the greatest problem confronting medicine. No other subject quite combines, in the same degree, the thrill of discovery and the prospect of beneficent application. So far as concerns the experimental reproduction of the disease and the understanding of the biological process involved, no more useful or more succinct general account can be recommended than that in the pages which follow.

ALEXANDER HADDOW

Chester Beatty Research Institute,

The Royal Cancer Hospital

(Institute of Cancer Research, University of London),

London, S.W.3,

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## PREFACE

THE final aim of cancer research is to elucidate the cause of the disease and hence find a rational approach to its cure. The problem has become so complex, however, its roots have spread into so many fields of scientific study, that the attack on it has to be confined at any one time, to one particular subject. In the present work on the chemistry of cancer two important questions have to be answered: in what respects and to what extent are tumours chemically different from normal tissue; and what are the causes of these differences. One approach to these problems has been the experimental induction of tumours by pure chemical compounds of known constitution. By means of these compounds—precision instruments in the hands of the biologist—we can interfere with the normal life of the cell and turn it into a tumour cell. The chemical carcinogen reacts in some way with a cell constituent, and a change takes place leading to malignancy. The nature of this change, its relation, on the one hand to the carcinogen, on the other hand to spontaneous cancer (the disease), is the problem of the chemical induction of cancer. Various subordinate subjects will also be discussed in the text; a possible relation between carcinogens and naturally occurring substances; the elaboration of carcinogens with certain characteristic groupings, or of such structural simplicity, as to facilitate an interpretation of their reaction with cell constituents; a direct observation of this reaction while it takes place and of the resulting change in the carcinogen (its metabolism); a possible approach to chemotherapy of tumours as related to chemical tumour induction.

The idea of writing this book was conceived after a lecture by an eminent cancer research worker on the Chemical Aspects of Cancer. A number of the physicians and medical students present expressed their bewilderment at the mass of chemical formulæ and data presented, which, though properly belonging to a study of the problem of cancer, was too specialised and novel an aspect of it to be covered by the usual medical course. The cancer problem, apart from its clinical aspect, is so closely connected with fundamental questions of growth, growth control and differentiation, that many medical men find it of interest. On the other hand, cancer research has grown and become specialised to such an extent that it is now almost impossible to keep abreast of the huge amount of literature on the subject. Consequently channels have become necessary to convey to the general medical reader an up-to-date survey of the achievements in the specialised fields, with as much discussion and critical evaluation as is possible at the present stage of cancer research. A number of excellent reviews on the subject of chemical tumour induction exist, but are somewhat too specialised to be of use to the general medical or scientific reader. Reference is made in the present work to some of these reviews and a list of the more important is presented at the end of the text. References are given, and collected at the end of each chapter, to the papers which throw most light on the subject under discussion; but it is not claimed that the bibliographies are exhaustive.

The attempt has been made as far as possible to present the subject in the form of a coherent story, to discuss experiments and observations in the light of hypotheses or theories which they support or oppose, and to discern interrelations between theories and patterns or structures of

knowledge, as they are built up or emerge. Isolated experiments or observations, so far as they bear no significant relation to the present theories and hypotheses, have not been discussed.

Though primarily designed for the medical reader, this book may also be of use to the many scientists who are continually drawn into the field of cancer research, and who, as specialists in other subjects, may wish to obtain a background in the chemical aspects of cancer research. Finally, the author has endeavoured to meet the needs of the general scientific reader who requires a survey of the present position.

The scope of the work has been limited to the experimental induction of tumours by extrinsic chemical means. By extrinsic are meant those substances not derived from the organism itself, such as the sex hormones, but chemicals deliberately synthesised in the laboratory for tests on experimental animals. The hormonal induction of tumours is not discussed in detail because hormones are present in the normal organism, the occurrence of cancer being determined less by the hormone itself than by factors such as genetic susceptibility; the emphasis is thus shifted from the chemical to the biological viewpoint. Nevertheless, certain aspects of hormonal induction of cancer are discussed as far as they touch on a possible biosynthesis of carcinogens in the organism.

As has been mentioned, emphasis is laid on the causes and processes underlying tumour formation which can be brought to light by rational experimentation; for that reason, the industrial (as opposed to experimental) induction of tumours is not discussed at any length.

Chapter I offers in simple terms, an explanation of the meaning of, and interrelations between, the structural



formulæ representing the various compounds discussed. Chapter II deals with the results following the administration of a carcinogen, and includes in outline the biological aspects of the subject. A note of warning must be sounded about chapters IV and V. They represent mainly interpretations of observations and are largely speculative; new findings might possibly render them obsolete overnight. A note (Appendix II) is included on Inhibition of Tumour Growth and the Possibilities of a Chemotherapy of Tumours, subjects not strictly coming under the heading of 'Induction of Tumours,' but sufficiently closely related to the organic chemistry of cancer to warrant a short mention.

I am deeply indebted to Professor Alexander Haddow for his constant help and encouragement, especially in the early stages of the writing of this book; to Professor and Mrs. L. F. Fieser for their great and painstaking help in the correction of parts of the manuscript; to Professors C. Heidelberger and G. C. Mueller for critical discussions of the contents of the book; to Drs. Nancy Carlton-Smith and I. Hieger for their kind assistance in the preparation of diagrams and illustrations.

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G. WOLF

McArdle Memorial Laboratory,  
The University of Wisconsin,  
The Medical School,  
Madison, Wisconsin,  
1951.

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## INTRODUCTION

*The Problem.* Cancer research is concerned with the discovery of a cure of cancer. However, the peculiar nature of the disease has necessitated the subdivision of this main problem into a large number of subsidiary problems, each contributing its own partial solution. The final answer will be attained through a synthesis of all the contributing solutions. Here we are concerned with that branch of the subject which deals with the experimental induction of tumours in animals by chemical compounds. What is the specific problem of this aspect of cancer research?

‘Cancer is pathologically unique,’ writes Berenblum. It cannot be classed with any of the many other known diseases; it seems to be closely related to, and spring directly from, the fundamental processes of life itself. ‘The zoological distribution of the disease—and the occurrence of somewhat analogous tumours in plants—is so wide as to lead us to suspect that the neoplastic change . . . has in its nature something fundamental in biology, and is one to which almost every cell is liable in appropriate circumstances’ (Haddow, 1944).

The most significant characteristic of living matter is its high degree of organisation, serving to maintain and perpetuate itself. This organisation is attained through growth and differentiation; firstly, by the highly organised and orderly accumulation of matter in the formation of the cell, the unit of living matter; secondly, by organised growth through strictly controlled and severely limited division of cells to form tissues; thirdly, by differentiation of growing and dividing cells into specialised organs.

Growth is controlled, and differentiation takes place, through the action of unknown forces or properties within each cell, probably connected with the functions of the hereditary substance of the chromosomes. Tumour growth is unique as a manifestation of living matter in that it escapes this purposeful organisation which characterises a living organism. The subservience of the part to the survival of the whole is abolished, 'the somatic cell, as it were, reasserts its individuality' (Haddow, 1944). The tumour cell, though originally derived from a normal cell, has irreversibly escaped the control of those forces which govern normal cell growth. It grows at a rate and in a manner in no way serving the needs of the organism as a whole, and generally at its expense, until the organism succumbs. The tumour is not a hostile parasite, but stems directly from a normally growing cell. In cancer we find the singular phenomenon of a trend towards a condition of disorder, disorganisation and de-differentiation through an invasion by intensely alive cells created by the living system itself.

The problem of cancer, therefore, is much wider and more general than merely the discovery of a cure. Its solution requires answers to the questions: What makes a cell grow in one particular way and no other, and arrests the growth at one particular point and no other? What are the forces and properties of the cell which control and organise growth? A disturbance of these forces or properties is set up in the cancer cell. A comparison between normal and tumour growth, between the normal and the tumour cell, and the discovery of the essential way in which they differ, may lead to a recognition of these forces and properties of cells—the very core and essence of living matter.

An investigation of normal or tumour bearing organisms can be undertaken at various levels: it may concern itself with gross morphological changes of tissues or organs; with morphological changes of single cells, or parts of cells (e.g., the nucleus); or looking closer still, with the molecular, or chemical, approach which traces differences in cells to differences in chemical constitution of the molecules which make up the cell. In the present state of knowledge, the molecular level is the most fundamental, because at this level biological observations can be most fully explained and organised into laws. Hence the chemical approach to the problem of cancer has the greatest significance. Put into the language of chemistry, the problem would be posed thus: in which way (qualitatively and quantitatively) do the molecules and their interactions in the tumour cell differ from those in the normal cell? What constitutes the essential chemical character of the tumour cell? These questions are closely linked to the problem of the properties of growth control and differentiation (lost by the tumour cell), since in the final analysis the governing and controlling factors of normal cells will be recognised as chemical in nature.

A more important question for the chemical approach is the following: what is the mechanism of this change from the normal to the tumour cell? This question touches directly on the principal problem, the cure, for if we can find the way in which the transformation takes place, we may be able to reverse or control it. Besides, a tumour regression initiated through an interaction of an administered chemical substance (a drug) with a tumour-cell constituent of known chemical constitution, seems the most plausible way in which one could envisage a cure.

In 1911 and 1915 two discoveries were made which proved to be of momentous value in the search for a solution of the cancer problem: a virus able to induce cancer in chickens was discovered by Rous; and the fact that chemical substances of coal tar can produce tumours in any part of the body of the experimental animal to which they are administered, by Yamagiwa and Ichikawa. The latter discovery puts the cancer investigator into possession of pure chemical compounds of known constitution which enabled him to upset at will the equilibrium of forces and factors, so far unknown, that bestow on the cell its ability of organised growth. Whereas previously he had to rely on observations of clinical cases or, at best, on transplantation experiments, he can now use the two cancer inducing agents, the chicken sarcoma virus and the chemical carcinogens, in an infinite number of designed experiments. He can attack the problem from the position of the biologist and investigate the interrelations between tumour induction and changes in the affected cell or organism, the influence of heredity, internal environment (e.g., hormonal influences) and external environment, and nutrition. He can concern himself with the agent itself and modify it in such a way as to throw some light on the cell constituent it reacts with, on its mechanism of action; or study the microscopic changes it elicits at the site of application, or its course through the organism (its metabolism). If he can ultimately elucidate the way the agent acts, its point of attack within the cell, the chemical changes it brings about, all the factors involved in the process of carcinogenesis, then he will also know something about the balance of forces and properties controlling normal cell growth which the carcinogen disturbs. There lies the problem of the chemical induction of cancer.



*The Method.*<sup>1</sup> The aim of cancer research is the cure of cancer. Since the control of normal cell growth in the organism seems to be effected through chemical means, the most likely agents for inhibition and control of tumour growth might also be chemical in nature. This trend of thought led to an approach now known as the Chemotherapy of Cancer (see also Appendix II, p. 227). This frontal attack on the problem is generally carried out in the following way: reports are received from clinicians that certain drugs have brought some measure of relief to cancer patients, or from investigators who by chance found certain chemicals to cause tumour regressions in experimental animals. The cancer research worker then takes the particular compound and subjects the molecule to many dissections and variations, in order to improve its healing power. Each new compound so obtained is then tested again on tumour-bearing animals or cancer patients. Consequently, large series of compounds are prepared and studied on the basis of what often seems to be very slight evidence. Other investigators go even further and test large numbers of compounds chosen only because they are readily available or because some of their molecular groupings bear a resemblance to those of certain cell constituents, vitamins or drugs. Random experimentation such as this, for which the subject of study is chosen almost by chance alone, differs greatly from the usual methods of scientific inquiry which have been developed with singular success through several centuries. Scientific progress is rarely made through the random collection of a large number of observations and the derivation of generalisations therefrom.

<sup>1</sup> The author is indebted to Prof. K. R. Popper, of London University, for the ideas on scientific method expressed in this section, though Prof. Popper is not responsible for the way in which they are here presented.