

The Biologic Basis of Cancer Management

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Forewords

THIS new book by Doctor Homburger has an extremely refreshing new viewpoint. It is important that pathologists have a broad understanding rather than a narrow one of the disease cancer, and this book in that respect, I believe, fulfills the purpose of Doctor Homburger to cover the broad field of cancer. He has done so in a most remarkable fashion in that the complexities of the research problems have been woven with clarity into the clinical approach, the treatment, and pathology. He has the remarkable capability of simplifying the problem to an extent that these unrelated disciplines are understandable and the problems that remain to be solved can be seen with better insight. To me he has not oversimplified these relationships and has well documented the viewpoints of the various disciplines by a well-chosen bibliography.

LAUREN V. ACKERMAN, M.D.
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THE plan underlying Doctor Homburger's treatment of the subject of cancer management is original and constructive.

By recognition of the complex biologic influences underlying and affecting the origin and development of the many types of cancer, the research worker or clinician is placed on a firm foundation of experimental reality from which he will not have to retreat.

The importance of such a stable base in a great expanse of rapidly increasing knowledge is obvious and is essential to a balanced and coordinated appreciation of the whole subject of cancer prevention, diagnosis, and therapy.

Investigators naturally are intrigued by factors in cancer etiology that

they can manipulate and analyze. Experimental and environmental influences quickly demand and easily receive prompt and enthusiastic attention and description. It is salutary and sobering to remember that they must be translated into terms of an intracellular process of uncontrollable biologic activity before their part in carcinogenesis is understood.

Clinicians welcome evidence of therapeutic agents which obstruct, delay, or control the development of the disease. Great programs of research to find such agents are under way, and even greater efforts are on the horizon. It is imperative that clinicians also remain constantly aware of the fact that cancer is a part of the reaction of its host's cells and tissues to intrinsic unbalance of function within that individual.

Underlying all of this, as Parts I and II of Doctor Homburger's book continually emphasize, are the inherited and transmitted differences in intracellular capacity for metabolism and reaction.

It is by due appreciation of each other's field that biologists, pathologists, chemists, physicists, and clinicians will acquire an over-all sense of proportion concerning the cancer problem. Toward that goal Doctor Homburger's book, both in concept and in content, has made a significant contribution.

CLARENCE COOK LITTLE, Sc.D.

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IN spite of advances that have been made in the control and treatment of cancer, the incidence of the disease is increasing, probably because of the increase in life expectancy throughout the world. Because it is increasing, a worthwhile treatise on the subject is commendable. Doctor Homburger's contribution, *The Biologic Basis of Cancer Management*, is particularly valuable because the author is both a cancer investigator and an internist. Most works on cancer are written by pure scientists, pathologists, surgeons, or radiologists, and it is unusual and significant to have a work written by an individual whose original training has been in the fundamental sciences and in internal medicine. It is perhaps understandable why internists generally have not been interested in cancer, because until relatively recently most cancers have been treated either by surgical extirpation or by destruction with irradiation. However, since cancer produces many systemic changes of a general nature in the host, internists should be interested in cancer patients and are becoming more interested in cancer, particularly because of the increasing availability of chemotherapeutic agents in cancer therapeutics.

Doctor Homburger discusses cancer in a very scholarly manner and without any preconceived ideas. The etiology of cancer and the various factors which are responsible for the development of cancer are discussed in detail with voluminous references made to original investigations. A valuable part of the work is that at the completion of each chapter, in which both experimental and clinical phases of the subject are considered, there is a summary on the correlation of clinical and experimental findings, giving the reader a résumé of Doctor Homburger's deliberations on the particular subject and demonstrating the areas in which there is correlation or lack of correlation in the experimental and clinical investigations. Because Doctor Homburger has done considerable investigation himself, he is in a particularly advantageous position to evaluate both the clinical and the experimental results.

All the factors that are known to produce and influence cancer are carefully considered in detail and their values assessed.

I have known Doctor Homburger for a number of years and have been greatly impressed by the character of the work he has done. I know of no one better able to prepare a treatise on the biologic basis of cancer treatment. I am convinced that this monograph will fill a real void which has existed for some time and that it will bring about a better understanding and correlation between the experimental investigations in cancer and their clinical application. Whereas the book will be of immense value to those interested in cancer research, it will also be of inestimable value to all physicians interested in and treating cancer.

ALTON OCHSNER, M.D.
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Preface

THIS book relates some of the fundamental knowledge of neoplastic disease and places it in perspective with the clinical problems posed by cancer. The major subjects discussed are the recognized causes of cancer, its natural behavior, its diagnosis, treatment, and prevention. Under these principal headings there are presented recent advances in biology, experimental pathology, biochemistry, cytochemistry, and physics, and the relation of studies conducted in these many disciplines to the clinical problems of the patient.

In addition to the inherent complexities of cancer, which defy rapid progress of knowledge and improvement of cancer management, there are two correctable difficulties hampering advances in these fields. These are the wide gap between new fundamental discoveries and their applications in cancer prevention and treatment, and a lack of understanding between the various disciplines that concentrate their efforts on the cancer problem. Only those clinicians who are well informed about present-day fundamental knowledge of cancer are in a position to evaluate quickly the significance of new discoveries and to perceive their pertinence to clinical cancer management. Only scientists who know the nature of the clinicians' problems and who have a thorough grasp of the thinking of their brethren in other disciplines are likely to understand and to cooperate with those working in fields outside of their own. An easily readable source of fundamental and clinical information is therefore much needed and may contribute to a better understanding and closer cooperation between clinicians and research people and among scientists themselves. This book should render it easier for everyone interested in the cancer field to acquire knowledge on many phases of cancer research and of the principal public health and clinical problems.

Although specialists in any one field may take issue with that portion of the book covering their area as being overly simplified and too rigidly organized, they may derive benefit from reading the other sections. The very

characteristics that arouse their criticism will enable them to assimilate readily that which has been written about areas of which they know little.

If I had wished to publish a collection of perfect reviews, I would have invited co-authors of eminence in their own fields, as I did in editing *The Physiopathology of Cancer* (1953),* to whom the specialist could refer for a review of his own specialty. This book, on the contrary, is an attempt to present the current landscape of cancer knowledge in broad strokes, outlining an impression of the whole. In art this kind of picture cannot be created by patching together many miniatures, no matter how perfect. In science and education no symposium of reviews, no matter how well done individually, can convey the broad background that every specialist should have in order to see his own work in its proper perspective.

To gain such a general view requires years of concern with a given field of endeavor. Even if they tried, some of the best specialists could never acquire it without aid. The very traits which render them good scientists, or even great ones, prevent many of them from seeing the whole. To achieve this requires a certain detachment and broad vision which are diametrically opposed to the attributes of perfectionism, narrowness of mind, and tubular vision which are the prerequisites for success as a specialist in this age of excessive specialization.

For those who know nothing or little about cancer, such as medical students entering the field or physicians and surgeons who may possess considerable clinical knowledge but have not kept up with research developments or any scientists entering the cancer field, the approach taken in this book presents an introduction to cancer as a disease entity and a biologic phenomenon.

This is the true nature of cancer. It is not merely an incidental phenomenon and subject for study in surgery, medicine, gynecology, and radiology but is a major disease having a broad fundamental base and necessitating for its best treatment the clinical science of oncology, which is born from interdisciplinary cooperation among basic scientists, surgeons, radiologists, pathologists, and physicians.

In this sense this book is intended as a guiding text for those medical students whose schools have followed the spirit of the suggestions made by the National Advisory Cancer Council in 1947,† which form the basis for the federal teaching grants-in-aid now received by most schools for the improvement of cancer teaching. This concept holds that cancer must be considered as a disease entity and that its understanding and management can best be taught in a vertical (cancer course) fashion.

* Paul B. Hoerber, Inc., New York, 1953 (2nd ed. in preparation).

† *J. Natl Cancer Inst.* 8:1-6, 1947.

In carrying out the teaching duties of a cancer coordinator, I soon found that there were no texts conveying the present-day knowledge of cancer research and management in readily understandable form and set out to fill this need with the present book. I have been guided in planning and writing it by the questions that about one thousand medical students have asked me since 1948. I have been stumped, intrigued, and sometimes appalled by these questions, but they have taught me what students want to know.

Many colleagues in cancer research have been helpful, and every chapter has been reviewed and criticized by a friend whom I thought most competent in the field discussed.

My sincere appreciation for their advice and help goes to Doctors J. Aub, C. Berman, P. Bernfeld, C. G. Child, III, F. Duran-Reynals, S. Farber, W. H. Fishman, E. H. Frieden, W. U. Gardner, W. C. Hueper, and D. Karnofsky.

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For their challenging, forthright criticism and continuous needling for more information, I thank my summer assistants, the medical students Milton S. Grossman and Erney Maher.

The author is especially grateful to Doctors Lauren V. Ackerman, Clarence C. Little, and Alton Ochsner not only for advice and help but also for each having contributed a foreword to this book.

A work that transcends the boundaries of the conventional disciplines inevitably will be criticized by those ubiquitous defenders of the past who believe in the orthodoxy of rigid specialization and traditional academic departmentalization. In its formative stages the idea of *The Biologic Basis of Cancer Management* was indeed rejected by a publisher because of the opinion of eminent consultants that no one person could write such a book. It is always dangerous to write a book, as Job knew when he said "My desire is that mine adversary had written a book." There are even greater pitfalls when an author ventures beyond the confines of his own specialty. With this in mind, the manuscript was submitted to leaders in the classic disciplines of pathology, biology, and surgery, and it appears that they agree that this effort to bring together, with one personal point of view, the present status of cancer problems in many disciplines has succeeded and that even the specialists may derive profit from it.

When one reviews a vast field such as modern cancer knowledge, he owes a debt of gratitude to the many before him who have labored to compile reviews and monographs on the subject. No man can read in detail all the original literature in as many fields as have herein been covered, and he

must rely heavily on the critical selections and analyses done before him. It would lead too far to refer here to the many reviews frequently consulted. They are quoted in the bibliographies, together with those original papers that seemed particularly useful and interesting to those who might wish to increase their knowledge at the sources.

The most gratifying aspect of this job of writing has been the constant need for a new personal point of view while compiling the book. For more than a year, a deliberate effort had to be made to read no longer merely for personal instruction the reports of those who have advanced our knowledge, but to have constantly in mind the intellectual needs of those who will continue to advance our science in years to come.

It is hoped that I have succeeded in forging a constructive link in the cancer field between the past and the future and that some of the intellectual stimulation and gratification that I experienced while writing this book will likewise be enjoyed by the reader.

F. H.

Bar Harbor, Maine

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Part I

THE ETIOLOGY OF CANCER

1

Occupational and Environmental Causes of Cancer in Man

INTRODUCTION

THE causes of most human and many animal cancers are still a deep mystery. However, there are a number of instances in man and in experimental animals where the causation of neoplastic disease is well understood. In man the best examples of cancers with known causation are certain occupational cancers such as cancer of the bladder induced by aniline dye derivatives and certain hereditary neoplasms such as retinoblastoma. In animals this is true, for instance, of spontaneous cancer of the breast in DBA and C3H mice. This is equally true of experimental cancers produced by chemical carcinogens such as methylcholanthrene, butter yellow, etc. In the case of neoplasms caused by viruses, such as the chicken leukoses and Rous sarcoma, papillomatosis in rabbits (Shope, 1933),* and the leukemia and maxillary gland tumors of certain strains of mice, well-defined and clearly responsible causative agents are involved.

Even in these relatively simple and to some extent artificial situations it soon becomes apparent that besides the carcinogens, viruses, or other incitors of neoplasia, there are other factors at play that may determine the eventual development of a neoplasm or may cause certain organisms to resist the development of cancer even though the causative agent is present. Often the known carcinogen will be ineffective in one species but effective in another. As is the case with the milk factor in murine cancer of the mammary

* A list of references for each chapter will be found at the end of the book.