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Microbial Testers

Probing Carcinogenesis

edited by
I. Cecil Felkner

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Probing Carcinogenesis

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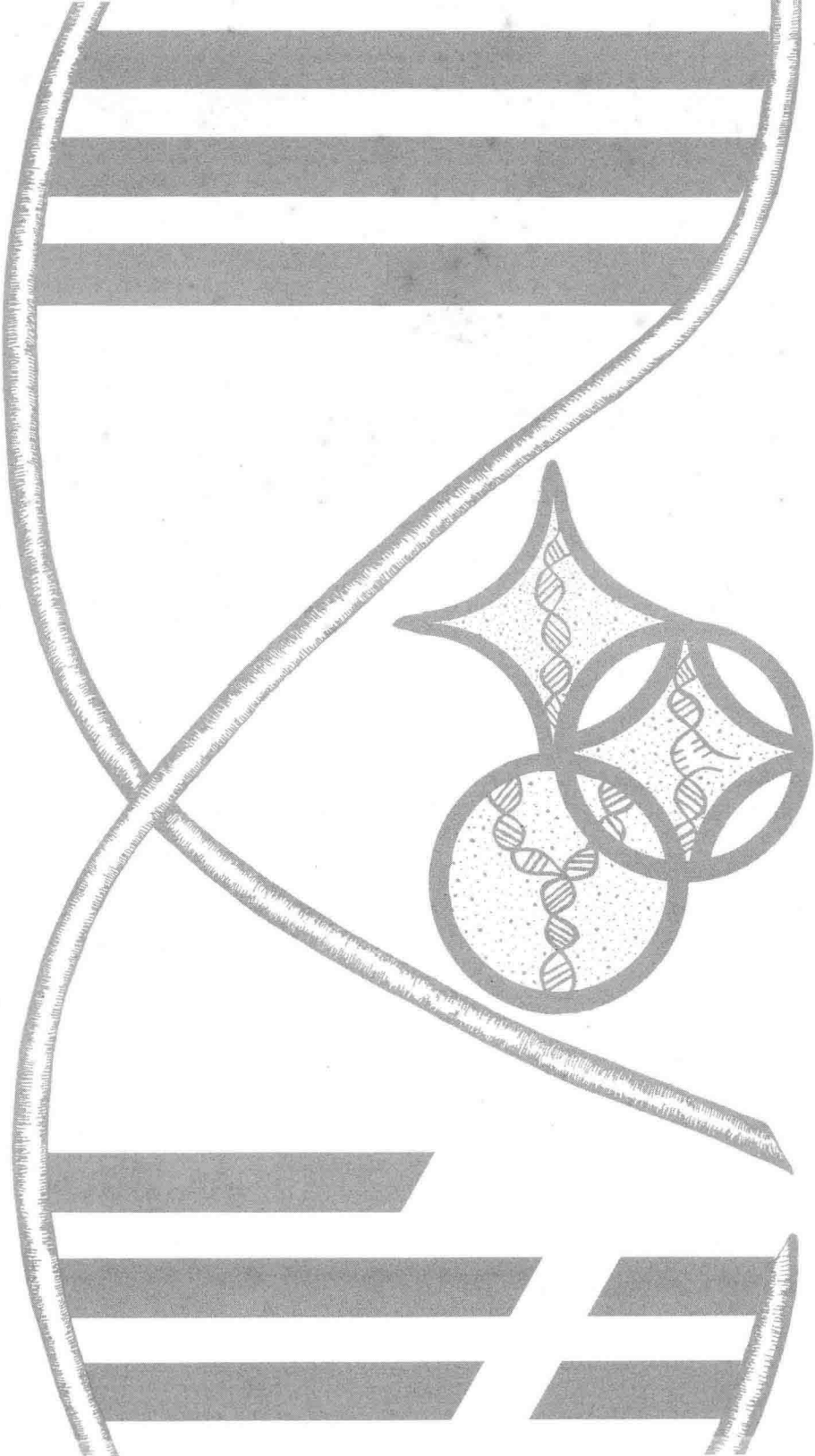

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FOREWORD

Emphasis on this compilation of essays in Felkner's Microbial Testers: Probing Carcinogenesis is a thrust in preventive medicine. In our essentially artificial environment there are working and living arenas revealing an interesting list of common substances suspected of causing cancer; and perhaps, more importantly, due to our environment we have adopted life styles and habits with known carcinogenic overtones. The emphasis in the text is to study microbial tester systems (and sensitive scientific instrumentation) as a means of detecting small traces of organic or inorganic chemicals, with important directional points toward implementation of cancer prevention.

If, in a rapid screen, a carcinogen is detected as a mutagen either directly or indirectly, there is an excellent possibility of pinpointing the chemical as a link in the events leading to a potential neoplastic problem. To identify the different chemical contaminations is the thrust of this book with deciphering the cost/benefit ratios and informational transfer to the human organism being the next logical steps from this basic science.

Bold leadership is needed in the oncology scientific community to test and then activate the conceptualization of cancer prevention. This differs from the research upon cancer cause and/or mechanisms of cancer metabolism. If we are being unwittingly exposed to conditions, materials, or chemicals, directly or through social habit patterns, a tester system is of inestimable help. This is particularly so if the system(s) is comparatively inexpensive, swift, and reasonably active in transferring knowledge of mutagenicity to carcinogenesis.

While the microbial tester system is basic and fundamental to health maintenance, leadership in the application and interpretation of this information may be difficult.

Iatrogenic issues must be faced; drugs or agents used to cure or palliate cancer may cause cancer. Cigarette smoking and, indeed, the physical agents associated with sunbathing are a social behavioral science issue. Colonic neoplasms may reflect in causation a sequence of interacting carcinogens and cocarcinogens, including dietary factors, all of which need to be unraveled.

The microbial tester system represents a rapid system to detect mutagens which cause DNA damage and have a high likelihood of being carcinogenic. The latency of the neoplastic process in the human being and the length and expanse of studies in animals makes this system very important to our health and the health of our progeny.

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PREFACE

This book is intended to give an account of the primary evidence for our current belief that environmental agents acting at the cellular, subcellular, and molecular levels can be detected and identified by carefully engineered microbial genetic systems. One should not, however, be led to the conclusion that identification of a suspected etiological agent as being one with mutagenic, DNA-damaging, or other genetic activity will necessarily associate it with oncogenic properties. Rather, a broader concept which is the underlying theme of this book should become apparent. This is the widely accepted theory that agents such as radiation and certain classes of chemicals which are reactive with nucleic acids may induce a sequence of events that lead to oncogenic, teratogenic, reproductive, and many other types of deleterious genetic effects. These genetic effects may be perpetuated through either somatic or germinal cell lines culminating in such dramatic expressions as cancer, birth defects, inherited metabolic or physiological diseases, and atherosclerosis.

The approach that we chose for this book is a relatively simple one that orients the reader through a series of four parts, each of which should provide conceptual building blocks for the next. Briefly, these include molecular and cellular mechanisms, design and construction of the assays, identification of potential pitfalls and suggestions for their resolution, and some examples of practical problems for which microbial assays have been or might be used.

This book has been prepared primarily for the scientist who is interested in the broad interdisciplinary areas of genetic toxicology, oncology, teratology, and in general environmental protection monitoring. It is hoped that the concepts and systems described will suggest to the reader unique ways to develop additional and more effective approaches, and assays to solve these problems which are potential sources of human suffering and economic drain.

As editor of this book, I wish to express my sincere gratitude to the authors who so generously contributed their valuable time and expertise. I wish to pay a special tribute to two of my former mentors whose guidance was particularly important to my interest in the present topic. To Professors Charlotte Auerbach and Orville Wyss, I am especially grateful. Finally, I would express my gratitude to Linda, my wife, not only for designing the opening page of the book, but also for her understanding during my many hours of labor.

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INTRODUCTION

On first inspection, the contents of this book might lead the reader to conclude that the topics covered are too diverse to be interrelated. This is because on the one hand microbial detectors are discussed, while on the other hand there is the matter of chemical carcinogens. In addition, there are chapters which deal with chemical and molecular biological concepts while still others focus on the relationship of diet and nutrition to cancer epidemiology. This could cause one to assume that a central focus might be missing. In order to reconcile these potential confusions, it is desirable to explain how these parts have a truly important interconnection.

To approach the subject of chemical carcinogenesis, it is clear that a multidisciplinary approach is required. To this end, it is perceived that bringing together varied aspects of research should ultimately lead to the prevention of cancer in humans. Therefore it is reasonable and proper that the carcinogenesis and mutagenesis processes should be the "center of the stage." However, in the world of reality they cannot stand in isolation in a manner likened to pure mathematics. This means that factors modifying these processes such as DNA repair; diet and nutrition; metabolism; epidemiology; and the formation, detection, identification, and quantification of environmental carcinogens/mutagens are subjects which are germane for our understanding of the subject.

Without a thorough understanding of the relevant chemical and molecular biological interactions of chemical and photochemical agents with macromolecular components, there would be no common ground upon which to relate carcinogenesis with mutagenic and DNA-damaging activities. It is

not enough to accept the theory that possession of both carcinogenic and mutagenic and/or DNA-damaging properties necessarily implies an identical underlying mechanism. Thus a sophisticated development of biochemistry, molecular biology, and photochemistry was the historic predecessor in the construction of microbial detector systems. But it should be recalled that microbes do not develop cancer or other bioendpoints that are restricted to mammalian life forms. Therefore, any extrapolations to a potential hazard for humans cannot be made directly without reference to animal models and/or relevant epidemiological data. It is now becoming well established that cancer epidemiology and even animal cancer models may be greatly modified by dietary and nutritional components. Thus, a given dose of a carcinogen may appear to be very potent in an individual with one nutritional status, but relatively weak in another whose dietary regimen is different. This makes it very difficult to relate the potency of an agent as a carcinogen to its potency as a mutagen or DNA-modifying substance, even if it can be shown that the mechanism by which an oncogenic response is induced is molecularly identical to mutation induction.

There is a strong tendency for us to want precise answers to our queries rather than to seek guidance toward asking the right questions. Perhaps if we ask what questions might be answered about chemical carcinogenesis with the aid of microbial testers, then a unique focal point may emerge. First one might ask whether a chemical acting as a mutagen forms a molecular adduct that can be also shown to occur in the course of its carcinogenic action, i.e., a common chemical adduct formed through an identical molecular biological interaction. Next it would be important to know if metabolic pathways in humans and/or model animal systems form a reactive chemical species that is both the relevant carcinogenic and DNA-modifying and/or mutagenic agent. This cannot be assumed on the basis of an in vitro produced genetic lesion in the tester system and an in-vivo-induced carcinogenesis. So we ask the question, "Do the metabolic paths of mutagenic agents coincide with the oncogenicity in an exposed individual?" If the answer is no, then why do carcinogenic agents also induce mutagenic and/or DNA-modifying effects? If the answer is yes, then how does one make maximum use of this knowledge? Obviously the use of microbial detectors with liver or other tissue postmicrosomal fractions applied in vitro as a prescreen for environmental carcinogenic agents demands such affirmation. Therefore, it is desirable that the scientific community closely scrutinize correlations between the in vitro test systems and carcinogenic responses in animal models. Here, the relevant question is, "Do in vitro tests in general, and more specifically those using microorganisms, accurately predict carcinogenic activity?" How do those tests using microbes as detectors compare to strategies that include mammalian tests? Presently, this is a difficult assessment to make because the vast amount of information for making such analyses is more or less confined to the most widely applied systems, in particular, the Salmonella/microsome test. As in vitro battery systems are developed and gain widespread use, the answers

will become more certain. But these questions must be asked now rather than deferring them to some later time because the application of microbial tests is already incorporated into the guidelines developed by federal agencies for assessment of genetic damage by modifying activity of any given chemical agent involving the same course of events that lead to tumor formation and cancer. Such studies can then provide a substantial basis for the valid use of microbial test systems in cancer prevention and cancer epidemiology of humans.

In the fundamental and pragmatic senses, it would seem that the best hope for progress will be an interdisciplinary approach to chemical carcinogenesis. The first step would be to identify the related disciplines and bring them together in such a way that the knowledge in one arena fosters testable ideas in another. And so it is that carcinogens and mutagens take a "center stage" in this interdisciplinary book, drawing together a diversity of approaches to a related goal: prevention of human suffering from cancer.

Microbial Testers

Probing Carcinogenesis

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