BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume I: Principles and Practice

Edited by

Manfred E. Wolff

ImmunoPharmaceutics, Inc.
San Diego, California

A WILEY-INTERSCIENCE PUBLICATION

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Burger's Medicinal Chemistry and Drug Discovery

Dr. Alfred Burger

Preface

Did we know the mechanical affectations of the particles of rhubarb, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file which by rubbing on them will alter the figure of any of the wheels; we should be able to tell beforehand that rhubarb will purge, hemlock kill and opium make a man sleep.

John Locke, Essay on the Human Understanding, 1690

Drug discovery has its roots in the beginnings of mankind. Even our phylogenetic cousins, the chimpanzees, have been observed to chew certain leaves to alleviate gastrointestinal distress. Likewise, in the evolution of the early hunter–gatherer communities it was only a short step from gathering vegetation to be eaten to assuage the pangs of hunger, to gathering material to be ingested to diminish the pain and discomfort of illness or injury. Thus, drug discovery has been important in every society, whether in the primitive tribes of North America or Africa, in the advanced classical Egyptian, Greek, and Roman civilizations, or in the more recent cultures of Europe, Asia, India, and elsewhere.

Today we are in the midst of an explosive expansion in the organized, purposeful discovery of drugs—an expansion that has occurred in the fifteen years that have elapsed since the previous edition of this series. Three forces are responsible for this growth. The first is the dawn of the golden age of biology, the stunning progress that has been made in structural biology and molecular biology, and its impact on the drug discovery process. The second is the information processing and transfer revolution that has made it possible to utilize all of the older and contemporary knowledge effectively in our new information society. And the third is the dramatic increase in the size of the world pharmaceutical market.

Science has never been confined by geographic boundaries. But in the past fifteen years, globalization, not only of technology itself, but of an appetite for the fruits of technology, has proceeded at an ever faster rate—the revolution of rising expectations. Nowhere is this more evident than in the desire of individuals everywhere to have the benefit of the best drugs available anywhere. The result has been to triple the world pharmaceutical market in ten years to $145 billion in 1989, compared to about $50 billion in 1979. Only six countries, the United States, Japan, Germany, Italy, France and the United Kingdom, are responsible for $113 billion (78%) of this sum. These countries represent only a fraction of the world population, and it is obvious that even greater growth is probable. In the past, a substantial part of such increases has resulted from simple price elevation. But the drive for cost containment in healthcare will ensure that most future growth will come from innovative new products and from market expansion.

The widening of the world pharmaceutical market has resulted in two collateral expansions. The first is in drug discovery research and development, both in absolute magnitude as well as in proportion to

product sales. For example, global R&D spending of PMA member companies as a percentage of sales changed from about 9% in 1980 to more than 15% in 1990. In addition, the absolute magnitude of U.S. R&D spending by PMA companies rose from about $2 billion in 1980 to about $7 billion in 1989. These increases have resulted in a dramatic expansion in the growth rate of pharmaceutical R&D spending in the U.S., as well as in the EC and Japan. Adjusted for inflation, the real growth in U.S. pharmaceutical R&D spending during 1975–1980 was only 3.5% per year. By contrast, during 1980–1990, the period since the publication of the preceding edition of this series, it was nearly 11% per year.

A second collateral expansion driven by the rapidly widening world pharmaceutical market has been in the number of pharmaceutical companies in operation, and being newly formed. It is a remarkable fact that there are hundreds of these, principally in the U.S., but also in the EC and elsewhere.

That these companies are attractive to the sources of financial capital necessary for their existence and operation is due to their potential for new drug discovery, and to the expectation of substantial profits from the sale of these new drugs. For this reason, such companies collectively employ thousands of scientists in the drug discovery area—scientists in laboratories and research programs that did not exist only a few years ago.

Not only has the scope and magnitude of drug discovery efforts expanded greatly, but the complexity, management challenges, and human resource requirements of the task have been correspondingly magnified. The new technologies, molecular biology, computational chemistry, the new analytical methods, and others, have combined to produce a more intellectually satisfying and effective, albeit more complex process. At the same time, increasingly stringent regulatory requirements with respect to novelty, efficacy and safety have made the development phase following drug discovery a more difficult undertaking. It is important that these later hurdles be fully appreciated by those workers active in the earlier aspects of drug discovery.

During the past decade, these drastically changed circumstances surrounding drug discovery created a much enlarged group of individuals involved in the search for new drugs. That group comprises not only academic and industrial scientists in the disciplines of biology, biotechnology, chemistry, physics, pharmaceutics and mathematics, but also clinicians, regulatory experts, financial analysts, lawyers, managers, and of course students and postdoctorals in all of these areas.

For success in the search for new drugs, full and complete communication is necessary between these many different individuals and disciplines. Drug discovery is above all an interdisciplinary effort—a team effort. As such, a contract lawyer may need to be aware of issues involved in the receptor specificity of ligands. A chemist may need to be conversant with aspects of patent law. A financial analyst may need to understand the potential of 3D database searches. A senior manager may need to appreciate the timing requirements of clinical trials. In this volume we attempt to inform such individuals in all of these areas.

Because numerous new factors must be considered in drug discovery, and a variety of individuals with widely divergent backgrounds now take part in it, the prophetic words of John Locke, which appeared in past editions and are given again at the beginning of this preface, address only a part of the task. Indeed, there are cases now where an x-ray crystallographic image of an enzyme inhibitor complex satisfies Locke's requirement for knowledge of the "mechanical affectations" of the drug and the patient. But we know now that this is not enough—that we must also have knowl-

One Hundred Newer Pharmaceutical Companies

Advanced Tissue Sciences
Affinity Biotechnology
Affymax
Agouron
Alkermes
Alpha-Beta
Alteon
Amgen
Amylin
Anergen
Applied Immune Sciences
Arris
Athena Neurosciences
Autoimmune
Biocryst
Biogen
Biomatrix
Biomira
BioSurface
Bio-Technology General
British Bio-Technology
Cambridge Biotechnology
Cambridge Neurosciences
Cellcor
Cell Genesys
CellPro
Celtrix
Centocor
Cephalon
Chiron
CoCensys
COR Therapeutics
Cortech
Corvas
Creative Biomolecules
Curative Technologies
Cytel Corp.
Cytogen
Cyto Therapeutics
DNX Corporation
Emisphere
Enzon
Genelabs Technologies
Genentech
Genetic Therapy
Genetics Institute
Gensia
Genta
Genzyme
Gilead Sciences
Glycomed
ICOS
IDEC
IGI, Inc.
ImClone
ImmuLogic
Immune Response
Immunex
ImmunoGen
Immunomedics
ImmunoPharmaceutics
Isis Pharmaceuticals
LifeCell
Ligand
Liposome Company
Liposome Technology
Magainin
Matrix
Medarex
MedImmune
NeoRx
Oculon
Oncogene Science
Ogranogenesis
Osteotech
PerSeptive Biosystems
Procyte
Protein Design Labs
Regeneron
Repligen
Ribi ImmunoChem
Scios Nova
Sergen
Shaman Pharmaceuticals
Somatogen
Sphinx
Synergen
SyStemix
T Cell Sciences
Telios
Texas Biotechnology
TSI Corp.
Univax Biologics
US Bioscience
Vertex
Vestar
Xenova
Xoma
Zynaxis

edge of drug metabolism, toxicity, a means to demonstrate decisive clinical efficacy, and a host of other matters, in order to be able to discover new drugs. An attempt has been made to provide an overview of all of these areas in this volume, entitled "Principles and Practices".

In preparing this new edition of these volumes founded through the vision of Alfred Burger, an effort has been made to incorporate the new developments into the discussion in every place where it has been possible. In this first volume, particular attention has been paid to product development questions which should be considered early in the discovery phase. We begin with a consideration of the conceptual background of medicinal chemistry by Alfred Burger, and continue with the management of drug discovery and the accessing and protection of information and intellectual property. In the second section, product development issues that are important to the discovery process are reviewed—questions of ADME, toxicity and drug allergy, and clinical trial issues. In part III, the

extensive advances that have been made in the structural biology of drug action are considered. And in the final section, the technologies for drug discovery, largely developed in the years since the preceding edition, are examined.

As indicated above, we hope that this volume will prove useful to all practitioners of drug discovery as well as graduate students and postdoctorals with these interests. We hope also that it will inform those interested in other types of biological actions of chemicals and biotechnology products, such as the environmental toxicity of herbicides and pesticides, or the effects of food additives. And, finally, we hope that it will serve as a suitable introduction and companion volume for the specialized chapters in the other volumes of this series.

I wish to express my sincere gratitude to the many persons who have made this new edition possible. Most of all, I thank the dedicated, knowledgeable authors, who have given so generously of their time in order to pass their expertise on to others, and many of whom have shared with me the benefit of their own views on the general topic of drug discovery. They and others have helped me enormously in defining the scope of this first volume, but ultimately the responsiblity for any deficiencies in this regard is mine alone. I am grateful to the editorial staff of John Wiley & Sons for their longstanding interest in this series. I wish especially to express my sincere appreciation to Lisa Trout, who organized and kept track of the voluminous correspondence resulting from so many interactions, and who tactfully managed finally to get all the manuscripts out of the hands of the authors. And finally I thank my wife, Gloria, for her enduring support and sustenance for all of my efforts.

MANFRED E. WOLFF

San Diego, California
January, 1995

Burger's Medicinal Chemistry and Drug Discovery

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PART I
THE DRUG DISCOVERY PROCESS

CHAPTER ONE

The Conceptual Background and Development of Medicinal Chemistry

ALFRED BURGER

CONTENTS

1 INTRODUCTION

Medicinal chemistry had its beginning when chemists, pharmacists, and physicians isolated and purified active principles of plant and animal tissues and later from microorganisms and their fermentation products. Some of these chemicals had been associated with therapeutic properties in often ill-defined disease conditions. During the latter decades of the 20th century, the traditional dividing lines between biological, chemical, and physical sciences were erased, and new borderline investigations such as molecular biology, molecular pharmacology, biomedicine, and others began to capture the interest of medicinal scientists. Medicinal chemistry which had leaned on the classical fields of chemistry, especially organic chemistry, biology and some areas of physics extended new roots into these emerging topics. Problems in hitherto unapproachable chemical studies with therapeutic implications became accessible and revised the choice of researches to the benefit of all the scientific doctrines involved.

2 NATURAL PRODUCTS

The elucidation of the structure and function of natural products, especially those with a history of biological properties, has been an important incentive for organic

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chemistry. Learning how Nature handles the synthesis and degradation of such substances is a deeply fulfilling and exciting goal of organic and medicinal chemists and of biochemists. One can never stop marvelling at the ingenuity of Nature which creates unexpected and often amazingly novel structures by biosynthetic and degradative reactions. The apparent purpose of these metabolic chemical reactions is to rid the parent organism of unwanted or toxic substances. In some cases, toxic metabolites may be useful in protecting the organism against predators or environmental hazards. There is no support for the belief that natural metabolites of plants and animals are produced for therapeutic uses by humans, even though humans have learned to harvest and process some of them for the maintenance of their homeostasis.

Over the last 200 years, natural products have been screened by experimental biologists who devised increasingly meaningful animal models of clinical pathologies. More recently, *in vitro* inhibition data of enzyme systems have simplified some of these tests and deepened our understanding of the mode of action of drugs.

A limited number of natural products can serve directly as therapeutic agents although lack of specificity frequently limits their application in human and veterinary medicine and in analogous pesticidal and other uses in agriculture. However, their never-ending variety and novelty serves as a source of prototype compounds for molecular modification. By dissecting the structure of a natural product chemically, one arrives at its therapeutically significant molecular sections, the pharmacophores. The portions that can be deleted are of no interest as components of drug action; they are regarded as the result of the biosynthetic efforts of the parent organism to construct materials for its own metabolic or defensive purposes.

Some structurally relatively uncomplicated biocatalysts such as several hormones and vitamins were originally regarded as uniquely designed for their biological mission and chemists were reluctant to interfere. It is now hard to imagine what impact their first molecular modifications had on contemporary thinking (1–5).

3 MOLECULAR MODIFICATION

When synthetic organic chemicals overtook the number of natural products, synthetic compounds offered an opportunity to medicinal screening. Some kind of selection of candidate compounds had to be made because dipping blindly into the supply of millions of synthetic compounds would have put the lottery to shame. Therefore, synthetic derivatives and structural analogues of biologically interesting substances were tested first for activities associated with the "lead" compound. Such programs included the branching, lengthening or shortening of chain structures, the variation of the kinds and positions of substituents, the replacement of rings by similar cyclic structures, and other empirical molecular modifications within the framework of reasonably close analogy. Functional groups were replaced by similar reactive radicals and occasionally an unorthodox change was tried. Many of the alterations were dictated by synthetic accessibility in a given structural series, without regard to biochemical reasoning.

As could be expected, close structural analogues of a biologically active material had a better chance of being similarly active than more remote analogues. The batting average among random variations was and still is low, ranging from 1:5,000 to even 1:10,000 for elaborating a drug that can survive screening and preclinical evaluation. Such systematic molecular modifications are not profitable; nevertheless, they remain the principal approach to new drug structures. It is a monument to human patience that so many valuable drugs have been developed by this method.