A GUIDE TO THE CHEMICAL BASIS OF DRUG DESIGN

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PREFACE

The design of the chemical structure of biologically active compounds is guided by the techniques and working hypotheses of the field of medicinal chemistry. It is not yet a reliable enough discipline to permit absolutely dependable predictions of the profile of biological activity of a test compound, but a number of experiences and valid experimental pathways have narrowed down the choices of procedure from the randomness of earlier approaches.

This book singles out these experiences, primarily those that have advanced drug design, but makes no apologies for the failures and continuing uncertainties that beset medicinal planning. Foremost among the reasons for these uncertainties is our limited appreciation of the totality of the effects of chemical and physical properties on biological activity. Second, experimental biologists and medicinal chemists work on different facets of the relationships between chemical structure and biological activity, the underlying principle of drug design. Even in the best cooperative teams the two types of scientists emphasize different aspects of their procedures and ideas, aspects that are difficult to reconcile in a complete program of drug design. Although drug design has thus remained a compromise between different working hypotheses and approaches, it has reached a stage of being an overall guide to the activity, potency, and potential pharmacological utility of chemical compounds. The role of chemists in such joint research efforts is stressed in this volume.

This book was written in the course of one year. One cannot write during a crowded schedule and read the current literature at the same time. Therefore the reporting is up-to-date only to about 1980 overall, with a few additions of more current events.

One of the first casualties of retirement from active teaching duties is the loss of secretarial help. I was fortunate in getting the rough long-hand manuscript typed by the staff of the Word Processing Center, American Hoechst Corporation, Somerville, New Jersey, D. Merriman, Supervisor, and J. Van Elk, Coordinator. The final manuscript was typed at the University of Virginia under a grant generously furnished by John Wiley and Sons, my publishers. I am grateful for this grant and for the assistance of the typists.

Many ideas and examples quoted in this volume are results of a lifetime in medicinal chemistry. A recent source of information for data in this book has been the three-volume treatise on the subject edited by M. E. Wolff (John Wiley and Sons, 1979–1981). Grateful acknowledgment is made to this important publication.

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INTRODUCTION

My interest in the chemistry of medicinal agents originated when, in 1928, I did volunteer work in the Vienna laboratory of Professor Sigmund Fränkel, whose treatise *Arzneimittel-Synthese* had then reached its 6th edition. In 1929 I became a research associate in the Drug Addiction Laboratory of the National Research Council at the University of Virginia. There, in cooperation with the pharmacologist Nathan B. Eddy of the University of Michigan, our unit studied molecular modifications of morphine and analogs of structural fragments of this opium alkaloid, with the avowed purpose of separating analgesia and dependence liability in the resulting compounds. We prepared one series of compounds after another based on reactions of the allylic alcohol system of morphine and on hydrophenanthrene and similar ring systems containing the amino alcohol functions of this alkaloid. While running rather similar reactions hundreds of times in such serial syntheses myself, I worried about the lack of reasoning underlying molecular modification in those days. Therefore the early (1932) publications by Hans Erlenmeyer (1) on the application to drug design of Langmuir's (2) and Grimm's concepts of isosterism and Hinsberg's (3) ideas of ring equivalents came as a welcome revelation. Here was the first suggestion of a rationale for molecular modification, including a prophecy that molecular shape would come to be considered a prime condition for analogy of biological behavior. A few years later Schaumann (4) demonstrated the importance of steric similarity when he explained the analgetic* activity of meperidine on the basis of its structure, which represented an unorthodox fragment carved out of the skeleton of morphine.

Biochemistry entered the picture of medicinal chemistry—a designation unalterably associated with biochemical explanations of the mechanism of action of medicinal agents—with the demonstration in 1940 by Woods and Fildes (5) that many drugs act as antagonists to biosynthetic substrates. This idea caused a virtual revolution in the selection of "lead" compounds, since an apparently unending supply of biosynthetic substrates emerged from the

* The *Oxford English Dictionary* points out that the term *analgetic* for insensibility to pain is a better formation than *analgesic* and more parallel with *anesthetic*, total insensibility.

improved analytical identification of intermediary metabolites. Although the repeated discovery of odd structures as drugs during random screening continued to accompany the more logical selection of "leads" on biochemical grounds, the latter raised the level of confidence in the discovery of medicinal agents and offered an intellectually rewarding approach to work in this field.

By the 1860's pharmacologists (6) had staked out claims for the conception and actual laboratory preparation of experimental drugs, a preoccupation for which they were little suited by temperament or chemical experience. The split of pharmacology from chemistry came when the design of pharmacological experimentation and the explanation of physiological mechanisms was placed on a firmer theoretical foundation and absorbed the time, energy, and curiosity of experimental biologists.

As medicinal chemistry became more biochemically oriented, the borderline with experimental biology became less distinct. Medicinal chemists should have stopped at this point because they, in turn, were ill-prepared to and not inclined to carry out biological experimentation. Instead, very many medicinal chemists became parlor pharmacologists, that is, they began to talk and think about pharmacological experiments at the expense of efforts they should have spent perfecting chemical experiments and chemical working hypotheses. As more of them fell into this pattern that should have been reserved for conversations during coffee breaks, medicinal chemical symposia and lectures followed suit. It became customary at such research conferences to invite clinicians and physiological pharmacologists to report on the problems they encountered during pharmacotherapy. The chemists in the audience were barely familiar with biological and medical terminology. They had been brought up to master organic, physical, analytical, and biological chemistry, and only few had had a formal course in biology or pharmacology (this educational shortcoming has been ameliorated in the last decade). But these chemists felt that on top of perfecting chemical, statistical, and instrumental experiences with a direct bearing on chemical thought and experimentation, they should be able to participate in biological decision-making. It is indeed necessary for medicinal chemists to be able to understand their biological teammates, but they should not permit their valuable time to be dominated by problems to which they, as chemists, could not make a systematic contribution.

Pharmacologists have every obligation to talk and write about the responses of cells and tissues to drugs, to describe drug metabolism, and to devise the best laboratory tests to evaluate the activity and toxicity of a drug. Chemists listening to or reading about such discussions usually feel discouraged. What does one do to one's "lead" compound if it produces a given side effect? Should one introduce chemical substituents? Or make the molecule more rigid, or less rigid, or homologize it? Even if one only wishes to make a competitive drug with virtually the same activity profile as the prototype, discussions at the cellular or tissue level—let alone behavioral data in animals or humans—will not serve as guides for chemical planning,

design, or understanding. The only common meeting ground is the explanation of the mechanism of action of a drug in biochemical terms, in studies of the inhibition of enzyme systems, antagonism to substrates, and other chemical reactions. Such reactions might then serve as models for chemical work on the drug. This means that medicinal chemists should participate more actively in the work of biochemists and give it direction toward the study of drugs in normal and abnormal physiological environments.

One of the most intriguing questions in medicinal chemistry is, How did an original discoverer of a drug get the idea that a given chemical structure might have pertinent biological activities? Since this problem arises every time a disease entity is singled out for pharmacotherapeutic study, this volume collects at least some of the historically more important aspects of drug discovery and selected cases of unusual circumstances that led to prototype compounds with therapeutic properties, provided they teach us what to look for in similar circumstances.

In treatises on medicinal chemistry, the space allotted to the description of the clinical and experimental biological background data has grown, as it should, with the advancing scope of knowledge in these fields. But in accord with the increasing interest of medicinal chemists in biological experiments, many sections of these treatises now describe biological events that cannot be translated into biochemical or medicinal–chemical data. Therefore a voice should be raised in defense of medicinal chemistry and to point out the features that make it an interdependent and yet independent science.

In this book I have no intention of reviewing the whole field of medicinal chemistry. No attempt whatsoever is made to provide complete coverage. This has been done authoritatively by 82 experts in the fourth edition of *Burger's Medicinal Chemistry* (7). Instead, the book is limited to underscoring what chemical work has been done and still needs to be done in medicinal science. When necessary for an understanding of what the chemists can do, references are made to biological background and experimentation, but these references are as brief as possible and restricted to quotations from the published literature.

Much medicinal chemical work is a repetitive and parallel effort. Such studies are dictated primarily by commercial competition as well as by the hope that persistent modification will sharpen selectivity and reduce toxicity of almost every type of drug. Except in systematic surveys, they do not teach much. Therefore, this volume concentrates on the chemical rationale of medicinal science. It should give the readers an idea of what they can expect to encounter in the field and should guide them to existing texts, reviews, and treatises for more complete and systematic information. Many references are made to the three-volume treatise edited by Wolff (7). Reading the chapters in those books will provide the systematic and biological details that the present volume does not deal with.

The first chapter arranges the field of medicinal chemistry by historic

sequence of observations. From 1950 on, however, this arrangement becomes unfeasible for the whole field because of the explosive simultaneous developments in many laboratories. Consequently, in Chapter 2 the most important events are described according to disease entities, and then the various new aspects of drug design are examined. This scheme is expanded in Chapter 3 so that a few instructive topics may be studied in somewhat greater detail. Subjects still in a purely empirical stage—such as drugs to control aging—are not treated because they cannot teach any chemical rationale, at least not yet. The experimental pharmacological details that a biologist must know are restrained, because medicinal chemists should not pose as parapharmacologists.

Throughout the book it is assumed that the reader, a medicinal scientist or student of medicinal chemistry, is familiar with many aspects of this subject. Therefore detailed explanations of facts, nomenclature, and well-known data that form the backbone of medicinal science are not given. Chemical formulas are shown where necessary for a quick assessment of a structural type, but they are not shown where a chemical name in the text is self-explanatory to a trained chemist or graduate student.

1

HISTORY OF MEDICINAL CHEMISTRY

1.1. EVOLUTION OF THE DISCIPLINE

Medicinal chemistry is the branch of chemistry that deals with the discovery, design, and development of therapeutic chemical agents for use in clinical and veterinary medicine. It deals with the relationships between chemical structure and biological activity, the identification of drug metabolites, and the biochemical explanation of the transport and actions of prophylactic, therapeutic, and curative medicines. The chemical concepts of medicinal chemistry have also permeated the fabric of biology, genetics, medicine, toxicology, and pest control.

The term "medicinal chemistry" evolved hesitatingly in the United States in the 1920's and even more slowly in other countries. Previously, colleges of pharmacy and research departments in the pharmaceutical industry had called their chemical sections "pharmaceutical chemistry," and a few conservative departments still adhere to this practice. It was recognized that "pharmaceutical chemistry" might be confused with "pharmaceutics," which deals with the formulation and the coating and finishing operations of a drug product in the apothecaries and in the industry. In addition, the ever closer ties of drug design with biochemistry and biochemical explanations of drug action made a change in designation advisable. With the appearance since the 1940's of several text and reference books, major journals (*Journal of Medicinal Chemistry, European Journal of Medicinal Chemistry*), several monograph series (e.g., *Progress in Drug Research*) and the *Annual Reports in Medicinal Chemistry*, the name "medicinal chemistry" has become firmly established. The last vestiges of confusion with medical chemistry, that is, analytical and diagnostic chemical procedures, were removed in Europe when frequent national and international symposia on medicinal chemistry were initiated there. The term "pharmacochemistry" has not found application in English-speaking countries (8).

This book was conceived as an overview of the mission of *chemists* in all the processes that lead up to the discovery and development of drugs.

Close cooperation between chemists and biologists is of the essence for this mission. However, the chemical identification, characterization, and preparation of biologically active materials—and most of all, the ultimate decision about structural changes that promise greater potency or a more acceptable spread between activity and toxicity—rest with the chemist.

Most accounts of the history of medicine give full credit for the discovery of drugs to experimental and clinical pharmacologists. This is still done in current reports on medicinal discoveries, both in medical journals and in the news media. When a pharmacologist tests an *existing* drug for a new activity unrelated to its established use and finds one in such trials, he is indeed the discoverer of this new application. But when a new substance is submitted for specified biologic tests, the chemists who dreamed up and prepared the material are recognized for their intellectual acumen and technical skill. Since the screening of large numbers of chemicals is time-consuming, expensive, and wasteful, any chemical or physical method that shortens this tedious process should be credited prominently as a contribution to the ultimate success in the search for medicinal agents.

It is not uncommon to delve into antiquity or the Middle Ages for the roots of medicinal chemistry, or iatrochemistry as it was called. However, the inventive and practical input into drug discovery and development practiced in those early days did not approach our present concept of the field, and the explanation of drug action was relegated to supernatural beliefs. The description of crude botanical drug powders and extracts is part of what has been called pharmacognosy in modern times. The use of natural materials and inorganic substances reported by alchemists at the end of the Middle Ages represented essentially the dawn of pharmacology and toxicology but harbored little chemistry. It would stretch the imagination if one classified the Swiss alchemist Paracelsus (1493–1541) (9), the Dutch van Helmont (16th century) (10) or Sylvius (17th century) (11) as ancestors of biochemistry and thereby as forerunners of those who try to explain the mode of action of drugs. The few chemical operations of alchemists that could be considered to bridge the transition to more modern science were mostly restricted to the use of inorganic elements (As, Au, Sb) and compounds.

1.1.1. Relation to Pharmacology

In 1876, the pharmacologist Rudolf Buchheim of the University of Giessen wrote that "the mission of pharmacology is to establish the active substances within the [natural] drugs, to find chemical properties responsible for their action, and to prepare synthetically drugs that are more effective" (6). This definition would now be applied unhesitatingly to medicinal chemistry. Pharmacology occupies itself with Buchheim's further statement that it "study the changes by the drug in the organism and then explore the possible influence of such changes upon pathological conditions." This dichotomy is more than semantics. Experimental biologists are ill-prepared by experience

or practical inclination to search for new chemicals, let alone to synthesize them or prove their structures; but without test chemicals they cannot verify the validity of test methods they have devised for a given disease entity.

Chemical thought processes have evolved slowly over the decades of therapeutic discovery. These ideas have at their center two requirements of medicinal chemistry: One is to find prototype ("lead") compounds that can provide an entry into a given area of drug research. The second is to rationalize and pinpoint molecular modification and avoid the almost senseless empirical choice of candidate compounds that characterized molecular modification before 1935 and gave it a low rating in the minds of some scientists. In both approaches considerable refinements and progress have been made by applying modern theoretical considerations of organic and physical chemistry to medicinal problems. This minimizes having to make assumptions in biology because, in spite of all efforts to unify physical and biological sciences, the increasing complexity of these sciences has separated them further in solving problems common to both. To be sure, all biology is based on chemistry, but the ladder reaching from fundamental biochemical metabolism to the structural explanation of macromolecular biological events has not yet been found in most cases.

Empiricism has characterized all efforts of medicinal science. As an example, one might read logic into the discovery of iodine (12) and its use in the treatment of goiter. But iodine was used first not for thyroid diseases but as a topical antiseptic (13), a use for which it has survived since 1839. The later connection of iodine and goiter was based on chance clinical observations. So much for iodine as an essential trace element; others such as chromium (14) have not yet even found a biochemical niche, except, perhaps, in insulin resistance.

1.1.2. The Role of Natural Products

The many methods practiced by medicine men and tribal doctors to treat illnesses in all parts of the precivilized world do not qualify as pharmacology or any other biomedical designation. In fact, many "drugs" conveyed to us by medicinal folklore had little to do with their alleged therapeutic purpose, because diseases were often misdiagnosed. Nevertheless, they provided important sources of natural products that centuries later could be extracted, purified, and identified. Natural products have remained valuable sources of potential drugs. They must have arisen from metabolites very similar to those found in the mammalian organism and therefore should be recognized more easily by mammalian biosites than some unrelated, totally unnatural chemicals. In addition, their structures are often novel and unexpected and are apt to arouse chemists out of their traditional thought patterns. Even so, natural products chemistry is organic chemistry, often at its very best, but it is not medicinal chemistry, which is motivated by biological activity.

One has to be a confirmed teleologist to assume that natural products

have been placed in plants or animals as sources of therapeutic agents for other animal species including humans. The majority of natural products probably represent biosynthetic intermediates or end products, often stored away in tissues where they are least in the way of the fundamental metabolic processes of the organism. Some natural products are toxic to animals, such as dicoumarol which causes the sweet-clover hay disease in foraging cattle, or the toxins of the barracuda which exert their action when the fish is ingested by humans. Similarly, the toxic action of the fungus *Claviceps purpurea* has been known for centuries to lead to epidemics of miscarriages and psychotic episodes. Some of these poisons, when purified and administered in judicious doses, have been used as therapeutic agents, but only after considerable chemical manipulation.

Some natural plant products serve as repellents to insects and other predators, but at least in one case a biogenetic relationship has become known. Some insects synthesize 6,7-dihydro-5H-1-formylpyrrolizine as a pheromone and use pyrrolidine alkaloids from *Crotalaria, Senecio,* or *Eupatorium* as biosynthetic sources for this purpose (15). Less causative relationships are seen in tannins that are toxic to insect herbivores. Tomato and potato plants produce proteinase inhibitors when attacked by chewing insects; these inhibitors affect the digestive processes of the insect and are accumulated by a putative plant wound hormone called proteinase inhibitor-inducing factor. 2-Tridecanone from a wild tomato inhibits feeding by the tobacco hornworm. Other defense agents against insects include cadinene, a sesquiterpene, and myrcene, a diterpene, which protect Douglas firs from budworm attack. A naphthoquinone derivative from the tropical medicinal shrub *Plumbago capensis* inhibits molting in several lepidopterous agricultural pests and inhibits an enzyme involved in the biosynthesis of chitin. Polyacetylenes from Compositae (daisies, black-eyed susans, marigold, fleabane) are toxic to mosquito larvae. One of these, α-terthienyl, is more potent than DDT in insects exposed to light. Leaf damage or UV irradiation of plants brings about the synthesis of antifungal and antibacterial phytoalexins; in soybeans these agents also deter feeding on the plant by the Mexican bean beetle, but in high concentrations the phytoalexins are very detrimental to the soybeans ("suicide response") (16).

1.1.3. The Role of "Lead" Compounds

Before synthetic organic chemistry hit its stride, natural products were the sole source of experimental medicinal materials. Their activities were almost always recognized by pharmacologists before chemists attempted to purify the active principles. At least one major American pharmaceutical company based its operations on this principle until 1950. They did not investigate the chemistry of any natural product—alkaloids, steroids, vitamins, hormones—unless pharmacologists had established the usefulness of the substance in medicine. Only then did organic chemists undertake the purifi-