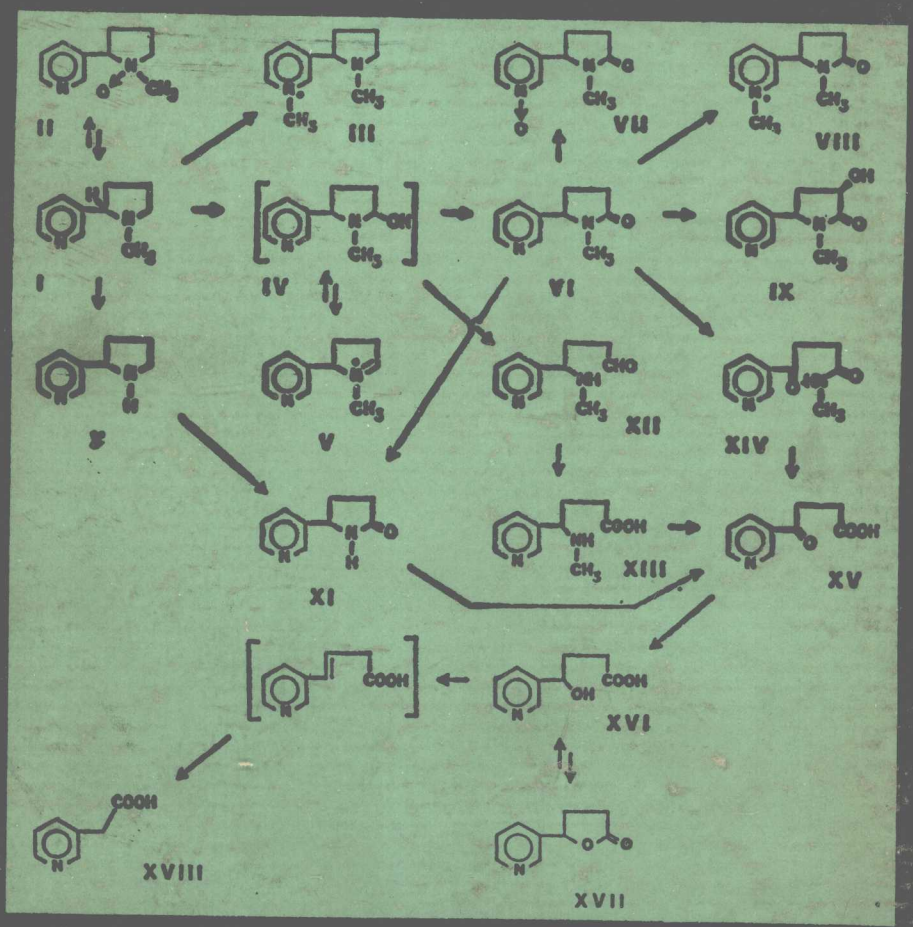
Drug Metabolism

CHEMICAL AND BIOCHEMICAL ASPECTS



DRUG METABOLISM:

CHEMICAL AND BIOCHEMICAL ASPECTS

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MARCEL DEKKER INC. New York and Basel

MARCEL DEKKER, INC.

270 Madison Avenue, New York, New York 10016

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 75-26114

ISBN: 0-8247-6371-8

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

DRUG METABOLISM:

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FOREWORD

Cocktails at the Savoy Hotel in London are served in no posh lounge. There is no dim, indirect lighting. And there are no divans to sink under your weight. Instead, drinks are served briskly, in an old-fashioned, brightly lit room, to people seated in straight-backed chairs.

One evening in September 1972, three of these chairs were occupied by Dr. Peter Jenner, Dr. Bernard Testa, and me. We talked mostly about a review which they planned to write on the influence of stereochemical factors upon drug disposition. Dr. Testa and Dr. Jenner also discussed the possibility of their writing a book on drug metabolism. Of course I encouraged this venture which, as I recall, appeared increasingly feasible as the Savoy service continued.

In March 1975, the typed manuscript was in my hands. My first reaction was awe at the magnitude of the effort. Immediately, I started to read the manuscript and soon found myself darting from section to section to learn what the authors had to say about subjects and compounds of special interest to me. At the end of the day, I toted the heavy opus to my car and drove it home. There, on a long dining room table, I separated the chapters and read several of them. I have been referring to this work ever since.

Reflections on this volume by Drs. Testa and Jenner have brought to mind three other authors.

James Conant wrote his classic text on organic chemistry in his own style. He had no opening chapter on physical chemistry "to provide background" - and to discourage the student eager to learn a new discipline. Nor did Conant start his book with the alkanes which make dull reading. He began, instead, with the alcohols in order to excite the receptive mind of the student. Conant considered science and its technical application to be inseparable. In the foreword to his "The Chemistry of Organic Compounds," he said, "Both have been kept in mind in the writing of this book in order to give a true picture of the varied and fascinating ramifications of organic chemistry."

R. T. Williams wrote "Detoxication Mechanisms" in the Conant tradition. The classic volume on drug metabolism is systematic, qualitative and illustrated with lively examples. Williams pointed out that "the study of the biochemistry of foreign compounds offers an apparently unlimited field of research when one considers the number of organic compounds now in existence and the number of different species of animals and plants in which each of these compounds could be studied." Williams, incidentally, disposed of aliphatic hydrocarbons in half of a page.

Testa and Jenner sustained the Conant/Williams tradition. "Drug Metabolism: Chemical and Biochemical Aspects" has commendable purity. It contains no opening chapter on pharmacokinetics or methodology. Indeed, the entire volume is undiluted with such material. Instead, it treats the chemistry and biochemistry of drug metabolism with relentless thoroughness, with enthusiasm, and even with fondness. The writing is clear, the approach is systematic, the texture is entirely qualitative, and the interplay between theory and practice is omnipresent.

Testa and Jenner have added a dimension which reminds me of William Faulkner. They present drug metabolism from two vantage points. In Part 1, they deal with chemical aspects of drug metabolism. And in Part 2 they return to reconsider the chemistry from a biological standpoint. The reader experiences this revisiting phenomenon throughout the book as he is directed backwards or forward to review some subjects in another light. These shades of Faulkner are most welcome in a scientific work! I suggest that you deal with this volume as with cocktails at the Savoy - appreciatively, under a bright light while seated in a straight-backed chair.

Frederick J. Di Carlo

INTRODUCTION

The effects of drugs on living systems have been studied by generations of pharmacologists, but the subject, far from being exhausted, continuously displays new horizons. The reciprocal of such interactions, namely, the various influences of an organism upon drug molecules, were given little attention for many years. Progress in several directions was necessary for the maturation of the science of drug metabolism in the fertile soil of medicinal chemistry and also pharmacology. Among the important advances made were the development of new analytical techniques, the understanding of the importance of drug metabolism and disposition on biological activity, and, last but not least, the work of a few pioneers whose ideas were far ahead of their time, and on whose firm base most of the research in this field has advanced.

When considering a specific drug, the way it influences a living system depends not only upon the nature of that drug, but also upon its fate in such a system. On the other hand, this fate is both a function of the "active" living system and of the "passive" substrate. In other words, an organism is equipped with a set of structures (e.g., membrane systems) and of tools (enzymes) which will enable it to exercise a well-defined influence on the drug (distribution, biotransformation, elimination). Similarly, the drug molecule displays certain structural features and physicochemical properties (e.g., its ability to act as a substrate for a particular enzyme) which directly influence the way it is handled by the living system.

These two aspects of drug metabolism (the influence of the substrate, and the influence of the organism) provide a convenient approach to the study of this rapidly expanding field. The chemical modifications a drug molecule can undergo obviously depend upon its various functional groups and structural elements. Thus, the first part of this book reviews the chemical reactions encountered in drug metabolic pathways. We have tried to present a classification of pathways as complete as possible by discussing the vast majority of reactions encountered. For every reaction, the various functional groups known to be substrates are considered by means of suitable examples. These examples are not restricted to actual drugs, but include many types of xenobiotics (i.e., exogenous anutrient substances of synthetic or natural origin).

The simple situation of a drug producing a single metabolite is not frequent, and in general complex metabolic patterns of competitive and sequential reactions occur. This fact is taken into account by grouping the separately considered reactions of some drugs into metabolic schemes (Chapter 1.3). Other structural features of molecules apart from their functional groups are relevant factors in drug metabolism; such are stereoisomeric and physicochemical factors, which are reviewed in separate chapters.

To consider drug metabolism from the point of view of the organism is extremely complex simply because a living system is an infinitely more complex entity than a drug molecule. Living systems can be considered at various levels of organization. While not neglecting the higher levels (whole organism, specific organs), we

have chosen to lay the emphasis on the biochemical and enzymic level. It is indeed here that a fundamental understanding of the problems encountered at higher levels of organization can be gained.

When considering drug-metabolizing enzyme systems from a biochemical viewpoint, a logical discrimination is apparent between the nature of the systems involved and the influence of internal and external factors on the activity and integrity of these systems. Consequently, we first examine the nature, location, and development of drug-metabolizing enzyme systems with particular reference to substrate interactions. This approach is then enlarged by considering the effect of external agents on such systems (i.e., processes of enzyme induction and inhibition), and by considering the influence of physiological factors.

The liver has long been considered as the main site of drug-metabolizing activity. However, recent studies have brought to light considerable evidence of metabolic activity in other tissues and organs. In an attempt to rationalize the inferences of these data we devote space to a consideration of extrahepatic metabolism.

While other zoological classes are not completely forgotten, this book is almost exclusively devoted to mammals. Indeed, this group has provided the vast majority of data in the field, and it can be considered as qualitatively homogeneous.

Obviously, some overlap exists between the chemical and biochemical parts of this book. In fact, this overlap is desirable if the phenomenon of drug metabolism is to be comprehended coherently and globally. In order to facilitate the reading, key words are underlined. Choices had to be made, the criteria of key words selection varying from chapter to chapter and intending to reflect the theme of each chapter.

This present work is aimed at creating a fundamental awareness of the basis of drug metabolic processes to those entering the subject or to those who have worked at higher levels of in vivo organization. By so doing we hope that a wider understanding of problems encountered at all levels may be achieved.

Bernard Testa
Peter Jenner

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CHEMICAL ASPECTS OF DRUG METABOLISM

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CHAPTER 1.1. PHASE I REACTIONS

The metabolic pathways known as phase I reactions involve the transformation of specific groupings in a substrate molecule. New functional groups are thus created.

As a general rule, the resulting metabolite displays an increased hydrosolubility as compared to the parent molecule. This rule has been explained in terms of animal evolution, and is linked with the transition from aquatic to aerial life. Indeed, water becomes a precious element for nonaquatic beings. As a consequence, natural selection would tend to favor those species which eliminate nonnutritive foreign compounds with maximum water economy, and which have acquired enzymic systems able to chemically increase the hydrosolubility of a large variety of substrates.

The biotransformations of chemical groupings (phase I reactions) are conveniently opposed to the reactions of conjugation (phase II reactions) discussed in Chapter 1.2. Although direct conjugation is not infrequent, phase I reactions precede phase II reactions in the biotransformation of most compounds. The reverse situation (i.e., phase II preceding phase I reactions), although less common, is nevertheless documented by several examples.

From the chapters to follow, it is evident that the phase I reactions are many. This variety, however, is more apparent than real. We believe the fundamental mechanisms of drug metabolism to be few, but to take manifold aspects when seen through the kaleidoscope of the numerous functional groupings acting as substrates.

1.1.1. OXIDATIVE REACTIONS

Biochemically speaking, the animal body is a reaction vessel complex beyond our present understanding, but whose general principle is the controlled combustion (oxidation) of carbon and hydrogen atoms. Oxidation of the organic molecules containing these atoms is the most important source of energy of the animal organism, and it is therefore not surprising that oxidative processes predominate in the metabolism of drugs and foreign compounds.

The carbon atom being the most significant chemical element in organic molecules, and its chemistry as such being relatively simple, it is only classical to start with it. The logical sequence of oxidation converting hydrocarbon to alcohol to carbonyl to carboxylic acid is also tempting. For various reasons which we hope will become apparent in the text, we have chosen to deal first with the oxidation of oxygenated carbons, and only then to discuss the hydroxylation and other oxidations of hydrocarbon groups.