JACQUES DESCOTES

IMMUNO-TOXICOLOGY OF DRUGS AND CHEMICALS

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IMMUNOTOXICOLOGY OF DRUGS AND CHEMICALS

This book is dedicated to Christiane,
Jérome and Aurélie

Foreword

This book by Doctor J. Descotes represents an ambitious attempt to catalogue the published literature on the immunomodulatory action of xenobiotics (e.g. drugs, chemicals and biologicals). Dr. Descotes has attempted to catalogue the material in such a manner that the reader can quickly find pertinent information about the known immunological effects of almost any agent. A unique table format was selected which includes the species and strain of the test animal; route, dose and duration of exposure; endpoints measured and percent alteration of a particular function reported; and the statistical significance of the data. This type of format provides any scientist using this volume with sufficient information to quickly evaluate the validity of the data in the context of other studies using the same endpoint(s) and a reference to the original manuscript for a more detailed and critical evaluation of the data.

It should be cautioned that the information listed in this volume on immune alterations resulting from xenobiotics exposure has not been critically evaluated by a panel of experts, as is done during the preparation of the World Health Organization's IARC monographs. Thus the reader will have to make his/her own judgements regarding the appropriateness of doses selected; route and length of exposure; general or specific toxicities; morbidity or mortality encountered; reproducibility and sensitivity of immunological endpoints selected; and the statistical methods utilized for analysis.

This book should provide a valuable reference and laboratory aid for immunologists and toxicologists involved in both basic research on and safety evaluation of xenobiotics.

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Preface

Over the last few years, Immunotoxicology has turned out to be an important and fully recognized subdiscipline of Toxicology. A steady flow of scientific papers have demonstrated that a wide array of pharmaceutical drugs and environmental chemicals are indeed likely to alter the immune responsiveness of exposed individuals, the potential health consequences of which are a matter of growing concern.

The aim of this book is to bring together published data regarding the possible or established immunotoxicity of these compounds. Basic mechanisms and methodological approaches are covered but briefly, since several recent reviews and symposia have dealt extensively with these aspects of Immunotoxicology. This is therefore an attempt to encompass those toxic effects on the immune system, the endpoint of which is either an increased, a decreased or a qualitatively abnormal immune response. Whenever possible, correlations between experimental data and human clinical findings are offered tentatively despite our poor knowledge of many fundamental aspects of the problem at the moment. Such an indication should therefore be considered as a mere attempt to delineate some of these issues likely to deserve further investigation. Drug allergy per se is beyond the scope of this book and will be covered only when clear correlates can be found between animal and human reports.

I hope that this volume will be of some help to those specialists who still lack an extensive coverage of published information in the field of Immunotoxicology, by providing quick and easy access to such data. Finally, I wish to thank Dr. J.H. Dean and Dr. J.G. Vos for having contributed the introductory chapter.

JACQUES DESCOTES
Lyon, St. Jean d'Avelanne
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PART I

METHODS AND CONCEPTS IN IMMUNOTOXICOLOGY

Chapter 1

An introduction to immunotoxicology assessment

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1.INTRODUCTION

1.THE SCOPE OF IMMUNOTOXICOLOGY

Immunotoxicology can best be defined as the discipline concerned with the study of the adverse effects on the immune system resulting from the interaction of xenobiotics (i.e., chemicals, drugs and biologicals). These adverse effects may result as a consequence of: 1) a direct or indirect action of the compound (and/or its metabolites) on the immune system; or, 2) an immunologically-based host response to the compound or its metabolite(s), or to host antigens modified by the compound or its metabolite(s). Immunotoxicology can be subdivided into three main areas of research (Luxembourg, 1985): 1) the study of the altered immunological events associated with exposure of humans and animals to xenobiotics, including drugs not originally intended for immunotherapeutics or drugs developed for immunotherapeutics (whether synthetic, natural or biological); 2) the study of allergy and autoimmunity resulting from exposure to xenobiotics; and, 3) the implementation of immunological techniques (e.g., improved analytical methods including immunocytochemistry, ELISA, EMIT, and radioimmunoassays) into toxicology research.

2.HEALTH SIGNIFICANCE OF IMMUNOTOXICITY

The capacity of a large variety of xenobiotics to which man is exposed to cause different types of allergic sequelae (e.g., contact hypersensitivity, immunologic lung disease, hemolytic anemia, lupus erythematosus, other autoimmune syndromes) is well established (see 1,2). The frequency of such pathologies, as well as their importance in terms of human morbidity are well established. In addition, there is also ample evidence that a galaxy of xenobiotics to which humans and animals may be acutely or chronically exposed may potentially damage the immune system through a variety of distinct mechanisms. Given the sensitivity of the cells of