

Immunotoxicology and Immunopharmacology

Third Edition

Edited by

Robert Luebke

Robert House

Ian Kimber



TARGET ORGAN TOXICOLOGY SERIES

Series Editors

A. Wallace Hayes

John A. Thomas

Donald E. Gardner



CRC Press
Taylor & Francis Group

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DEDICATION

The third edition of *Immunotoxicology and Immunopharmacology* is dedicated to the memory of Professor Dr. Jef Vos. Jef was one of the founding fathers of immunotoxicology, and among the first to recognize that environmental agents may have adverse effects on the immune system. In his long career at the National Institute of Public Health and the Environment in the Netherlands (RIVM), he guided the development of many young scientists and lead established colleagues by example. His reputation as a first-rate scientist and his warm personal manner won him respect and admiration far beyond RIVM. His friends and colleagues are saddened by his loss, as we reflect on the impact he made on the science and the friendship he so freely shared with us all.

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Preface to the Third Edition

Although a decade has passed since the publication of the second edition of *Immunotoxicology and Immunopharmacology*, the issues and research priorities faced by immunotoxicologists and immunopharmacologists remain the same: identification of agents that modify immune function, determination of mode or mechanism of action, and translation of laboratory or clinical data into scientifically sound prediction of risk or benefit to the exposed population. In keeping with the tradition established in the first two editions, this edition provides comprehensive reviews of the mechanisms underlying immunosuppression, allergy and hypersensitivity, and autoimmunity. Advances in basic immunology, cellular and molecular biology and genetics since publication of the last edition have increased our ability to detect and characterize events that follow manipulation of the immune system. Therapeutic modulation of the immune system has increased dramatically in the last ten years, resulting in the development of therapeutic agents that target specific cellular and humoral molecules. Technical progress in the basic sciences has likewise aided assay development, and increasingly sophisticated methods adapted from basic immunology and cell biology have enabled investigators to determine mechanisms of immunotoxicity at the level of signaling pathways and gene transcription.

In the third edition, mechanisms of environmentally induced immunosuppression, allergy, hypersensitivity, and autoimmunity have been updated to reflect progress made over the last decade. Similarly, trends in risk assessment and in model development to detect and characterize immunomodulation are addressed directly in chapters dedicated to regulatory issues, and indirectly in chapters focused on mechanisms of immunotoxicity. In some cases, expanded coverage is given to topics discussed in previous editions. For example, two chapters are dedicated to immunotherapeutic proteins, another to dietary supplements and foods with immunomodulatory properties, and another to the current and potential future uses of genomics and proteomics techniques to identify and characterize immunomodulators. A section on wildlife immunotoxicity was added to address immunotoxicity across a wide range of biological complexity, from invertebrates to marine mammals. New to this edition is a section dedicated to interactions between the immune and central nervous systems, and the consequences of altered nervous system function on immune homeostasis.

This book will be of interest to toxicologists, immunologists, clinicians, risk assessors, and others with an interest in accidental or deliberate immunomodulation. Although few of the chapters are written on an introductory level, background information and citations for review articles are included in most chapters that will provide a starting point for individuals seeking additional information.

Robert W. Luebke

Preface to the Second Edition

Although the philosophy and design of the second edition are consistent with the first, many changes have been made to reflect the metamorphosis of this area from a subdiscipline of toxicology to an independent area of research that can best be described as “Environmental Immunology.” For example, chapters have been added that describe the role of immune mediators in liver, lung, and skin toxicity, in regulating drug- and chemical-metabolizing enzymes and in the immunosuppression produced by ultraviolet light, as well as immunotoxicology studies of non-mammalian systems. More emphasis has been placed upon the clinical consequences of immunotoxicity as well as on the interpretation of experimental data for predicting human health risk. A number of chapters from the first edition have been deleted, particularly those that provided descriptive overviews of the immune system, in order to limit the size of this edition while increasing the scope of immunotoxicology subjects.

Unlike the first edition, this book is divided into three major subsections, comprising immunosuppression, autoimmunity, and hypersensitivity. This division allows for a more comprehensive treatment of these important subjects with greater attention to test methods, theoretical considerations, and clinical significance. The section on immunosuppression begins with introductory chapters discussing consequences of immunodeficiency, human and animal test systems, and risk assessment. This is followed by chapters discussing various environmental agents, therapeutic drugs, biological agents, and drugs of abuse as well as immune-mediated toxicity that occur in specific organ systems. The second section is devoted to autoimmunity and includes discussions on the immunopathogenesis of autoimmunity as well as examples of chemical- and drug-induced autoimmune disease. The last section, which is devoted to hypersensitivity, has been greatly expanded from the first edition. This section begins with discussions on the clinical aspects of allergic contact dermatitis and respiratory hypersensitivity. This is followed by chapters describing mechanistic aspects of sensitization and the methods available for the toxicologic evaluation of chemical allergens.

This volume will be of interest to toxicologists, immunologists, clinicians, and scientists working in the area of environmental health. It should also be of interest to individuals involved in occupational health, safety assessment, and regulatory decisions. Although we assume that most readers have at least some understanding of immunology, we have attempted to prepare this book so that any individual interested in environmental sciences could follow it.

Michael I. Luster

Preface to the First Edition

Traditional methods for toxicological assessment have implicated the immune system as a frequent target organ of toxic insult following chronic or subchronic exposure to certain chemicals or therapeutic drugs (e.g., xenobiotics). Interaction of the immune system with these xenobiotics may result in three principal undesirable effects: (1) those determined by immune suppression; (2) those determined by immune dysregulation (e.g., autoimmunity); and (3) those determined by the response of immunologic defense mechanisms to the xenobiotic (e.g., hypersensitivity). The first section of this volume reviews the basic organization of the immune system and describes the cellular and humoral elements involved, the interactions and regulation of lymphoid cells, and their dysregulations that result in disease.

Toxicological manifestations in the immune system following xenobiotic exposure in experimental animals appear as alterations in lymphoid organ weights or histology: quantitative or qualitative changes in cellularity of lymphoid tissue, peripheral leukocytes, or bone marrow; impairment of cell functions; and increased susceptibility to infectious agents or tumors. Allergy and, to a lesser extent, autoimmunity have also been associated with exposure to xenobiotics in animals and man. Chapters are included in the second section which describe approaches and methodology for assessing chemical- or drug-induced immunosuppression or hypersensitivity.

Awareness of immunotoxicology was stimulated by a comprehensive review by Vos in 1977, in which he provided evidence that a broad spectrum of xenobiotics alter immune responses in laboratory animals and subsequently may affect the health of exposed individuals. Several additional reviews, as well as national and international scientific meetings, have reinforced these early observations. In several studies, alteration of immune function was accompanied by increased susceptibility to challenge with infectious agents or transplantable tumor cells, indicating the resulting immune dysfunction in altered host resistance. Clinical studies in humans exposed to xenobiotics have confirmed the parallelism with immune dysfunction observed in rodents. The latter sections in this volume describe studies with xenobiotics that resulted in immune modulation in rodents and man.

The sensitivity or utility of the immune system for detecting subclinical toxic injury has likewise been demonstrated. This may occur for one of several reasons: functionally immunocompetent cells are required for host resistance to opportunistic infectious agents or neoplasia; immunocompetent cells require continued proliferation and differentiation for self-renewal and are thus sensitive to agents that affect cell proliferation or differentiation; and finally, the immune system is a tightly regulated organization of lymphoid cells that are interdependent in function. These cells communicate through soluble mediators and cell-to-cell interactions. Any agent that alters this delicate

regulatory balance, or functionally affects a particular cell type, or alters proliferation or differentiation can lead to an immune alteration. One section of this volume is devoted to possible mechanisms by which xenobiotics may perturb lymphoid cells.

This volume should be of interest to toxicologists, immunologists, cell biologists, and clinicians who are studying mechanisms of xenobiotic-induced diseases. It should also be of interest to scientists faced with the challenge of the safety assessment of immunotherapeutics, biological responses modifiers, recombinant DNA products, drugs under development, and other consumer products. This volume should better prepare toxicologists for the challenges of the 21st century.

Jack H. Dean

Acknowledgments

The editors of the third edition thank the Target Organ Toxicity Series editors for their continued recognition of the need for an updated volume on immunotoxicology and immunopharmacology. We greatly appreciate the time, effort, and expertise of our colleagues who contributed chapters to the book, the patience of our colleagues at work, and of our families at home, who complained very little about the time spent editing this book.

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Part I

Immunotoxicology and Hazard Identification

1 Immunotoxicology: Thirty Years and Counting

Robert V. House and Robert W. Luebke

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INTRODUCTION

The science of immunotoxicology arguably began in the early 1970s, following the recognition of increased sensitivity to infection following exposure of test species, including guinea pigs [1], mice, [2, 3] rats [4], ducks [5], hamsters and monkeys [6] to various xenobiotics. Reduced resistance to infectious disease was a well documented consequence of primary and acquired immunodeficiencies, but a novel outcome of xenobiotic exposure, leading some to characterize xenobiotic-induced immunosuppression as “chemical AIDS.” Although the comparison was scientifically inappropriate, “immunotoxicity” was often thought of as synonymous with “immunosuppression” during the formative years of the discipline, although hypersensitivity, allergy, and autoimmunity were recognized as potential exposure outcomes. The first review in the field of immunotoxicology was published by Vos [7], followed in 1978 by the first symposium organized specifically to address this topic at the Gordon Research Conference on Drug Safety. The number of investigators and laboratories conducting immunotoxicology research increased significantly in the United States and Europe during the late 1970s and early 1980s. As research expanded during this period, many of the assays, methodologies, and approaches that are currently used to identify potential immunotoxicants were developed.

In 1984, the first international meeting of immunotoxicologists was organized by the Commission of the European Communities and the International Programme on Chemical Safety/World Health Organization in Luxembourg. This meeting, entitled “Immunotoxicology: The Immune System as a Target for Toxic Damage,” summarized the state of the science and defined immunotoxicology as undesired direct or indirect effects of xenobiotics on the immune system causing suppression, an immune response to the chemical or its metabolites, or alteration of host antigens by the chemical or its metabolites [8]. Approximately 80 scientists from around the world, from the fields of immunology, pharmacology, pathology, and toxicology, discussed approaches for immunotoxicity assessment in rodents and discussed several compounds recently shown to cause immunotoxicity.

Immunotoxicology has matured over the intervening three decades, gaining recognition as a subspecialty of toxicology, and the interests of immunotoxicologist have broadened to focus on modulation, rather than only suppression, of the immune system by chemical and physical agents. Several areas of investigation including allergic contact dermatitis, respiratory hypersensitivity, and air pollutant toxicology, which originated independently, were merged into immunotoxicology as it was recognized that all involved perturbations of the immune system. In this chapter we will briefly explore the multiple paths that the field’s progression has taken over time. This treatment is meant as a survey only, since adequate treatment of each topic requires more than a few paragraphs and many of the topics are discussed elsewhere in this volume or in recent reviews. Where appropriate, the reader will be directed to resources for more intensive coverage. Likewise, it is important to note that this survey will not take a strictly chronological approach since progress in all aspects of immunotoxicology has not been linear.

ORIGINS AND PROGRESS IN IMMUNOTOXICITY TESTING

THE TIER-TESTING APPROACH: SETTING THE COURSE FOR MODERN IMMUNOTOXICOLOGY

The majority of early publications that can be reasonably identified as comprising “immunotoxicology” reported altered resistance to infection in animals exposed to various environmental or industrial chemicals. Authors logically concluded that xenobiotic exposure suppressed immune function since the immune system is ultimately responsible for this resistance to infection. Subsequent studies demonstrated that suppression of various cellular and functional endpoints accompanied or preceded increased sensitivity to infection, and that administration of known immunosuppressants likewise decreased host resistance. The human health implications of these studies, that chemical exposure reduced resistance to infection, drove the initial focus of many immunotoxicologists on functional suppression, and provided the theoretical and practical underpinnings of immunotoxicity testing.

Although the experimental methods adopted by immunotoxicologists to evaluate immune function were those common to immunology laboratories, experimental designs were often ad hoc. This lack of standardization often made it difficult to compare chemical-specific results obtained in different labs and lead Dean and colleagues [9] to propose a “tier testing” paradigm. This approach was based, according to the authors, on the need for assays to be “relevant to the human experience and adaptable to certain practical considerations such as cost, reproducibility of data, ease of performance and application to routine toxicology studies.” Using these criteria, a tiered approach was developed with differential priorities: screening assays to detect immunologic effects (Tier I) and a comprehensive suite of assays to provide an in depth assessment of immune function and host resistance endpoints (Tier II). A battery of assays from the screening tier was subsequently assembled into a hypothetical and practical test battery to screen for immunological effects of a chemical with potential immunosuppressive properties. This approach was tested with encouraging results using the known immunosuppressant, cyclophosphamide [10], and the testing paradigm was then further refined [11,12].

From these conceptual and early proof-of-concept studies, the tier-testing approach made a significant practical leap when the approach was employed by the National Toxicology Program in an inter-laboratory validation study between NIEHS (Research Triangle Park, NC), Virginia Commonwealth University (Richmond, VA), Chemical Industry Institute of Toxicology (Research Triangle Park, NC) and IIT Research Institute (Chicago, IL); each laboratory evaluated the same chemicals, using the same set of assays [13]. In this effort, both descriptive and mechanistic assays were employed including hematology, selected organ weights (spleen, thymus), and histology of lymphoid organs. Functional tests in this tier include T-dependent IgM antibody formation, natural killer cell function, and lymphocyte mitogenesis. (Mitogen-driven lymphocyte proliferation has poor predictive power and has been replaced by lymphocyte phenotyping in current tier testing protocols [14]). The results of this exercise, as well as follow-on studies to determine the biological significance of the findings, resulted in a series of watershed

publications [13–15]. The results and concepts developed in these early efforts provided the basis for moving immunotoxicology assessment forward, and has been extensively reviewed [16–19].

Use of Tier-Testing for Industrial and Environmental Chemicals

The earliest defined immunotoxicology test guidelines were developed to assess pesticides, since these chemicals have significant potential for large-scale human exposure. In 1996, the Office of Prevention, Pesticides and Toxic Substances (OPPTS) of the U.S. Environmental Protection Agency (EPA) published *Biochemicals Test Guidelines: OPPTS 880.3550 Immunotoxicity* [20], which described the study design for evaluating immunotoxicity in biochemical pest control agents. The panel of tests included in this guideline was taken directly from the National Toxicology Program's tier-testing approach and includes routine toxicology tests, as well as functional evaluation of humoral and cell-mediated immune function. The document describes the actual testing procedures to be employed, but little guidance was provided for interpretation of test results. Thus, a second document was published concurrently entitled *Biochemicals Test Guidelines: OPPTS 880.3800 Immune Response* [21]. This companion guideline provides a rationale for evaluating pesticides for immunotoxicity, more detailed explanations of testing strategies, and additional details on mechanistic assessments, including host resistance assays and bone marrow function.

Whereas immunotoxicity evaluation encompassed by the 880 series of guidelines would be expected to detect suppression of innate, cellular or humoral immunity, the number of required tests would greatly increase the financial and resource costs of testing. In 1998, the Agency published *Health Effects Test Guidelines: OPPTS 870.7800 Immunotoxicity* [22], describing immunotoxicology testing for EPA-regulated, non-biochemical agents that fall under the regulatory requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 et seq.) and the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601). The testing approach mandated by 870.7800 reflects the more limited, case-by-case approach currently favored. Most notably, the functional assessment is limited to T-dependent antibody response (TDAR), natural killer (NK) cell function, and quantitation of T- and B-cells. The current (2006) version of the 7800 Immunotoxicity Guidelines calls for testing in mice and rats, unless data are available to show that absorption, distribution, metabolism and excretion are the same in both species. Although mandated for FIFRA and TSCA compounds, the guidelines call for exposure via the expected route of human exposure (oral, dermal or inhalation), and are applicable to a range of industrial and environmental chemicals. The U.S. EPA's Office of Air and Radiation, for example, requires that these guidelines be followed when air toxics are subjected to testing for immunotoxic potential.

Adaptations of the Tier-Testing Approach

Chemicals that do not fall under the testing requirements for pesticides may have immunotoxic potential. However, submitting all industrial chemicals for immunotoxicity

tier testing is impractical due to the expense involved and the numbers of animals that required. For this reason, microscopic examination of immune system organs has been used as a predictor of immunotoxicity, and as a trigger for functional testing. This concept was first explored by Shuurman colleagues [23], although it gained momentum from then until 2000, at which time the idea was developed in greater detail [24, 25]. Although the use of extended histopathology assessment as a routine immunotoxicology test was first widely adopted in Europe (due primarily to the inception of the regulatory document *Note for Guidance on Repeated Dose Toxicity (CPMP/SWP/1042/99)* [26], the approach has gradually gained support in the United States [27–29] and was incorporated in the ICH S8 immunotoxicology guidance (discussed below), in which histopathology plays an important role [30]. A recent study demonstrated that while the antibody response to sheep erythrocytes correctly identified 90% of known immunotoxicants in a dataset of compounds tested by the U.S. National Toxicology Program, extended histopathology correctly identified 80% of known immunotoxicants when minimal or mild histologic change in any tissue (spleen, thymus or lymph node) examined was accepted as evidence of immunotoxicity. However, mild change in any tissue also identified known negative compounds and tissues from vehicle control groups as immunotoxicants, whereas limiting calls to chemicals that caused moderate to marked tissue changes resulted in poor predictive performance, indicating that the criteria used to classify chemicals as immunotoxic must be carefully set to avoid high false positive and false negative rates [27, 28].

Seminal immunotoxicity experiments were conducted in rats [4], although the mouse became the preferred model, at least in the United States, because this species was commonly used by immunologists and reagents and inbred strains were readily available. However, the rat has traditionally been used in industrial chemical toxicity studies, and investigators worked to adapted testing methods [31] and performed comparative studies in mice and rats [32, 33], ultimately validating the use of rat as an alternative for immunotoxicity testing [34, 35]. This was followed closely by the publication of a collaborative study by the International Collaborative Immunotoxicology Study (ICICIS) workgroup on the use of the rat in immunotoxicology [36], which arrived at the same conclusion.

One other noteworthy development in the evolution of the tier-testing approach is the increasing use of sophisticated statistical analyses to evaluate the predictive value of data generated by these studies. Concordance analysis of NTP datasets provided the first insight into which tests were the most accurate in identifying immunotoxicants, and predicting changes in host resistance [15,16]. Others have used statistical methods to model various aspects of immunotoxicity testing and data interpretation. For example, immunotoxicity data for an individual compound are typically derived from several sets of animals, yet multivariate analysis is typically applied to datasets in which all endpoints are evaluated in all animals. However, Keil and colleagues [37] modeled the effects of obtaining data from different sets of mice and found that the purported disruption of the correlation matrices, critical to multivariate analysis, did not occur, indicating that not all variables must be derived from the same animal. This group also used multiple and logistic regression analysis to evaluate the relative contribution made by

individual effector mechanisms on host resistance endpoints and reported that moderate functional changes induced by an immunotoxicant predict altered resistance to bacterial or tumor cell challenge, although predictive endpoints were not necessarily those that immunologic dogma would suggest [38]. Shkedy and colleagues [39] reported success in fitting a nonlinear model to individual animal antibody responses to KLH to derive maximum likelihood estimates, which were then analyzed for treatment effects or using nonlinear mixed models to account for individual animal variability in antibody titer. Modeling efforts as described above may shape future testing methods by providing additional insight into modes and mechanisms of immunotoxicity, and the functional or observational endpoints that best predict changes in immune function.

THE EMERGENCE OF REGULATORY GUIDANCE

As methods to evaluate immunotoxicity became more established and evolved to the stage of standardization, these techniques became a potentially useful tool to evaluate specialized toxicity to the immune system from a regulatory standpoint. We have previously examined how the U.S. EPA was responsible for some of the first such testing guidelines; however, the road to acceptance of such guidance for pharmaceutical development in both the United States and Europe (and, to a less obvious degree, in Japan and the rest of Asia) has been much less straightforward. Calls for regulatory guidance began in the early 1990s [40–43], leading to publication of the first codified regulations for immunotoxicology in 2000. Current regulatory guidelines for immunotoxicity hazard identification are discussed in chapter 2 of this book.

Europe: Note for Guidance on Repeated Dose Toxicity

In Europe, safety testing for pharmaceuticals is regulated by the Committee for Proprietary Medicinal Products or CPMP. In October of 2000, CPMP published *Note for Guidance on Repeated Dose Toxicity (CPMP/SWP/1042/99)* [24]; although the primary purpose of this particular document was to describe an overall approach to safety testing of pharmaceuticals, it was important as the first guidance document mandating specific immunotoxicology screening for pharmaceuticals. An appendix in the guidance document describes a staged evaluation, emphasizing that information gained in standard toxicology evaluation can be useful as a primary indicator for immunotoxicity. Functional tests may be incorporated to gain additional information, first as an initial screen and then progressing to extended studies as necessary. The choice of assays to be used includes combinations of functional tests known to be predictive of immunotoxicity, as described by Luster and colleagues [14,15].

As the first published requirement for immunotoxicology evaluation of drugs, *CPMP/SWP/1042/99* predictably was met with a combination of resistance and confusion. Much of this was allayed in a Drug Information Association-sponsored workshop held in Noordwijk, The Netherlands in November of 2001. At this meeting, the intent of the guideline was clarified; a summary of this workshop, as well as an update, has been published [44, 45].

United States: Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs

In the United States, ensuring the safety of pharmaceuticals is the responsibility of the Food and Drug Administration Center for Drug Evaluation and Research (FDA/CDER). In October of 2002, CDER released a long-awaited document entitled *Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs* [46]. This document is arguably the most comprehensive of any published guidance, and includes detailed descriptions of immune system-related adverse drug effects, including immunosuppression, immunogenicity, hypersensitivity, autoimmunity, and unintended immunostimulation. The document also includes suggested approaches and methodologies to evaluate each type of adverse immune effects. Like the CPMP document (described above), the FDA/CDER guidance advocates the use of information derived from standard repeat-dose toxicity studies to provide early evidence of immunotoxicity, with subsequent evaluations to be rationally designed to use a minimum of animals and resources while deriving the maximum amount of information. Subsequent to the publication of the FDA/CDER document, the primary author of the guidance published a manuscript describing the implications of the guidance [47].

ICH S8: Immunotoxicology Studies for Human Pharmaceuticals

The requirement for immunotoxicity testing in the CPMP guidelines, and reliance on clinical data to trigger testing in the FDA guidelines resulted in differing opinions on the utility of routine testing [48, 49]. Recognizing the need to globally standardize these regulations, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) initiated the process of compiling this document. The guidance “provides recommendations on nonclinical testing approaches to identify compounds that have the potential to be immunotoxic and guidance on a weight-of-evidence decision making approach for immunotoxicity testing.” Similar to previous documents, the S8 guidance will apply to unintended immunosuppression and immunoenhancement, but will not address allergenicity or drug-specific autoimmunity [50–53].

BIOLOGICALS

Biologicals (i.e., therapeutics derived by biotechnology) present a unique challenge for immunotoxicity assessment for two primary reasons. First, many of these agents (such as cytokines, growth factors, etc.) are intended to modulate the immune response therapeutically, making it difficult to differentiate between efficacy and toxicity. Second, because many of these agents are proteinaceous, their introduction into a host can result in an immune response directed against the molecule itself; this can lead to alterations in pharmacodynamics or other adverse reactions. A detailed discussion of therapeutic biological molecules is presented in chapter 8 of this volume. One approach to testing protein immunomodulators was addressed by the International Conference on Harmonisation via the publication of *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

S6 [53]. This document includes sections on immunogenicity as well as a brief section on immunotoxicity evaluation. Notably, the use of a standard tier approach was rejected in favor of case-by-case screening, followed by mechanistic studies as necessary.

VACCINES

In the past, vaccines have received only slight notice from toxicologists, possibly from the naïve notion that the nature of these medicines limited their toxic potential. We are increasingly recognizing this to be untrue, and thus the appropriate regulatory agencies have formulated guidance documents governing safety testing of these intentional immunomodulators.

For example, European regulation of vaccines is described in the CPMP's *Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines* [54]. Therein, immunotoxicology should be considered during toxicology testing, and vaccines should be evaluated for their immunological effect on toxicity (e.g., antibody complex formation, release of cytokines, induction of hypersensitivity reactions, and association with autoimmunity). Each vaccine is to be evaluated on a case-by-case basis.

Responsibility for safety of vaccines in the United States belongs to FDA/CBER. One of the primary documents describing vaccine studies is *Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies* [55]. Animal immunogenicity is covered in detail in the document, although immunotoxicity is not specified as an area of concern. Another document, *Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications* [56], acknowledges the potential immunological reactions resulting from the vaccination process to exert unintended consequences. Specific guidance for actually performing such evaluations is not covered by any of these documents, but should be determined on a case-by-case basis depending on the regulatory circumstances [57,58].

THE LLNA: A CONCERTED EFFORT TO VALIDATE METHODOLOGY

While most published immunotoxicity testing guidelines are structured to detect immunosuppressants, hypersensitivity reactions are far more common. None of the assays included in standard tier-type protocols are appropriate for assessing the sensitizing potential of chemicals, and thus a specialized assay was required. Early testing strategies relied on tests in guinea pigs (see chapter 31), supplanted in 1989 with the murine local lymph node assay (LLNA) [59]. Over the course of the subsequent decade, Kimber and his collaborators amassed an impressive collection of studies demonstrating the utility of this assay for identifying contact sensitizers. In particular, inter-laboratory collaborations [60] demonstrated that the assay was sensitive, reproducible, and (most importantly) sufficiently robust to apply in a large-scale validation study. Therefore, The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) sponsored just such a study using the LLNA, which became the first assay

to be validated using their stringent criteria. The details of this process are too complex to review here, but the results have been published and are instructive reading [61–63]. Following validation, the LLNA became the standard assay for evaluating the sensitizing potential of chemicals and drugs. Detailed explanations of this assay and its use are covered in the OECD 429 guideline, *Skin Sensitisation: Local Lymph Node Assay* [64] and the U.S. EPA document *OPPTS 870.2600 Skin Sensitization* [65].

INTERPRETING LABORATORY ANIMAL DATA IN TERMS OF HUMAN RISK

While it is well established that immunosuppression can lead to an increased incidence or severity to certain infectious and neoplastic diseases, interpreting data from experimental immunotoxicology studies, or even epidemiological studies, for quantitative risk assessment purposes is problematic. This is particularly true when the immunological effects, as might be expected from inadvertent exposures in large populations, are minimal-to-moderate in nature, and values obtained for various immunological endpoints fall within a range considered to be normal for the population. Furthermore, detecting significant changes in rates of infection with common human pathogens in exposed populations is difficult against a background of infection in groups of individuals with no known exposure to immunotoxicants. Thus, the relationship between altered immune function and increased sensitivity or susceptibility to the types of infection likely to occur in individuals without primary or acquired severe immunosuppression has been the most difficult to establish. However, it is critical that a firm scientific basis for interpreting the outcome of immune function and host resistance studies in laboratory animals be established if results of Tier I and II data are going to be used to predict possible human effects as part of the risk assessment process. The infection risk posed by mild to moderate immunosuppression in humans, and interpretation of immunotoxicity data for human risk assessment, are discussed in chapter 3 of this volume.

ENVIRONMENTAL AND WILDLIFE IMMUNOTOXICOLOGY

Perhaps due to phylogenetic chauvinism, but as likely for more practical reasons, the evaluation of immunotoxicity has largely been confined to laboratory rodents, with the implicit (and often explicit) understanding that these mammalian species can serve as reliable surrogates for humans. This traditional approach may be somewhat myopic in that evaluation of species from chronically polluted sites may provide insight into the effects of chronic low level exposure to toxicants that may also affect humans. A variety of environmental pollutants have been evaluated for immunotoxic effects in non-laboratory species, including marine mammals, particularly seals [66, 67], birds [68], fish [69], and even invertebrates [70]. Although the level of immune system complexity is far different in invertebrates and mammals, many aspects of innate resistance to infection are phylogenetically conserved, and have been studied in detail. Assays developed by comparative immunologists and wildlife immunotoxicologists have been employed to

evaluate immune function in free-living species chronically exposed to environmental contaminants, and in laboratory-reared species under controlled conditions. Adverse effects observed in wildlife species often parallel those obtained when analogous endpoints are evaluated in traditional laboratory species. Thus, wildlife species may act as sentinel species for potential human effects [71] while simultaneously providing insight into the potential immunotoxicologic risk posed by contaminated sites to indigenous species. The three chapters in Section VI of this volume describe immune function and immunotoxicity in wildlife species, including invertebrates, selected vertebrates and marine mammals.

DEVELOPMENTAL, PERINATAL, AND REPRODUCTIVE IMMUNOTOXICOLOGY

For much of its history, immunotoxicology has used young adult rodents as the primary experimental species; this is logical, since the need to control as many variables as possible would suggest that a stable (i.e., mature) immune system would respond most reproducibly to outside influences such as toxic exposure. However, it has long been recognized that organogenesis and maturation represent periods of increased sensitivity and susceptibility to toxicants, and among the first immunotoxicity studies to be published evaluated the effects of gestational/neonatal xenobiotic exposure on the immune system [72,73]. As the evidence for increased sensitivity of the developing immune system mounted over the years, it was suggested that immunotoxicity studies should be included in standard reproductive toxicity screening studies [74], and that evaluation of immunotoxicity exclusively in adult animals may not predict effects in the developing organism [75,76].

In recognition of the increased vulnerability of the developing organism, both the U.S. EPA Food Quality Protection Act [77] and the U.S. EPA Safe Drinking Water Act [78] mandate that infants and children warrant special consideration in the risk assessment process. Immune system ontogeny and the sensitivity of the developing immune system to xenobiotics are discussed in detail in chapter 20 of this volume.

As was the case with tier testing, developmental immunotoxicology has been driven by expert workshops to reach consensus on the most important issues; three workshops were held in 2001 [79–81], and another in 2003 [82]. These workshops contributed to the development of a proposed testing framework to detect developmental immunotoxicity, which is described in detail in chapter 21.

FUTURE TRENDS IN IMMUNOTOXICOLOGY

UNINTENDED CONSEQUENCES OF THERAPEUTIC IMMUNOMODULATION

As noted above, the primary focus of immunotoxicology has been on suppression; many of the early techniques grew out of basic immunology research, in which the function of various components of the immune response was determined by selective manipu-

lation of these components, particularly in defining functional parameters critical to resistance to infection or neoplastic disease. However, the consequences of some forms of immunostimulation, including therapeutic manipulation of various components of the immune system, may be less obvious, but nonetheless adverse. Unfortunately, traditional testing paradigms are inadequate to determine these consequences; developing effective testing strategies is a major challenge of future immunotoxicologists since modalities for enhancing the immune system are increasing.

The recent rapid development of immunostimulatory therapeutics likewise has outpaced our understanding of the potential immunotoxicity associated with these drugs. One example is the unmethylated oligonucleotides (e.g., CpG ODN) that are being developed as Toll-like receptor (TLR) agonists for a variety of therapeutic applications. Although these molecules hold great promise, they have been associated with a variety of adverse reactions [83–87], and it is clear that novel testing approaches and assays will be necessary to understanding these reactions as development of these drugs progresses.

The adaptive immune response to most infectious agents is typically robust and includes a memory component that provides long-lasting protection against the specific agent. For most relatively innocuous agents that humans and animals are exposed to, this is sufficient to protect us. For the particularly dangerous organisms or their toxic products, vaccines (discussed below) are administered to provide protection without the risk of actual exposure. For most organisms and under most circumstances, this is sufficient. However, conventional adaptive responses may not offer adequate protection against biological warfare and bioterrorism agents, emerging biological threats such as methicillin-resistant *Staphylococcus aureus* or drug-resistant tuberculosis, or man-made organisms with yet undefined but potentially dangerous characteristics. As our understanding of the interaction between the innate and adaptive immune system improves, so does the potential to therapeutically manipulate the innate defenses to provide short-term, nonspecific protection. In this scenario, a therapeutic agent or combination of agents would be administered in advance (or immediately following) exposure to these threats [88,89]. Such agents include TLR agonists and other related pattern-recognition receptors [90] and molecules [91]. Application of knowledge gained from recent molecular and genetic immunology research has stimulated the development of additional classes of therapeutics that target very specific aspects of the immune response and may prove useful in the treatment of immunodeficiency and autoimmunity. Some of these agents have been subjected to clinical trials, and the efficacy and toxicity of these new therapeutic agents are discussed in Section II of this volume; protein-based immune response modifiers are presented in chapter 8 and immunostimulating biological molecules presented in chapter 9.

Finally, a particularly interesting ongoing challenge will be to understand the potential for “do-it-yourself” immune stimulation to have unintended consequences. There are now many herbal supplements, “functional foods” and other over-the-counter products that promise to boost the immune response and most are considered to be safe for use by the general public. Although there is limited published evidence of adverse immune system effects of these materials, some have been associated with autoimmunity [95,96]. See chapter 11 for a detailed discussion of the beneficial and potential adverse effects of nutraceuticals and functional foods.

USE OF TRANSGENIC ANIMAL MODELS

The technology for specifically engineering mutations in the immune system of laboratory animals will increasingly give investigators the ability to evaluate perturbation of the immune response. The promise of this technology for immunotoxicology was first described by Lovik [97], and a number of recent uses of this technology for investigational immunotoxicology have been described [98].

IN VITRO IMMUNOTOXICOLOGY

Current public opinion and ethical considerations have stimulated efforts to reduce the number of animals used to test the toxicity of chemicals, drugs and personal care products. However, only limited effort has gone into developing *in vitro* or *in silico* methods to detect immune dysfunction. This may be at least partially attributable to the sheer complexity of the immune response, although there has been sufficient progress to warrant continued investigation along these lines. The exclusive use of *in vitro* assays may always have limited utility as a replacement for functional assays [99, 100], although the European Centre for the Validation of Alternative Methods (ECVAM) has sponsored at least two workshops of international experts to devise testing strategies based on functional assays [101, 102]. Rather, future directions of *in vitro* immunotoxicology will almost certainly take advantage of proteomics/genomics technologies, as has already been explored with the so-called CellChip [103, 104] and adaptations of cell-based high throughput screening for biological activity as used by the pharmaceutical industry. At some point in the distant future, *in silico* methods might replace animal testing in certain cases [105].

APPLICATION OF GENOMICS TECHNIQUES AS TOOLS FOR HYPOTHESIS GENERATION AND MECHANISM OF ACTION STUDIES

Evaluation of xenobiotic-induced changes in gene expression as a potential method to identify and classify potential toxicants has been pursued by industry and regulatory agencies worldwide as a means to screen and prioritize chemicals for functional evaluation. The U.S. EPA recently released a white paper discussing the potential uses of genomic data for regulatory purposes and risk assessment at the agency [106], and in recent years laboratories have begun to investigate the use of toxicogenomics to detect and characterize chemical modulation of the immune response. Current goals of toxicogenomics, which would also be important in immunotoxicology, include hazard identification by comparing microarray results with analyses of SAR or animal bioassays, or risk characterization by coupling genomic data with exposure assessment or cross-species comparisons. Studies such as the multi-site collaborative project, begun in 1999 and sponsored by the ILSI Health and Environmental Sciences Institute Genomics Committee (<http://www.hesiglobal.org/Committees/TechnicalCommittees/Genomics/>), provide a template that immunotoxicologists may apply to reach these same goals. The

ILSI-sponsored efforts suggest that biological pathways can be identified consistently across platforms but direct gene comparisons are challenging, and that genomic data alone are insufficient and should be tied to a phenotypic anchor. A workshop was held in 2005 at the Environmental Protection Agency in Research Triangle Park, North Carolina, to address the potential of genomics techniques as an alternative or adjunct to traditional screening methods for immunotoxicity. The use of genomics techniques as a screening tool for immunotoxicity and as a technique to identify mode or mechanism of action was discussed, as was the use of genomics data in the risk assessment process. Workshop participants concluded that the use of genomics holds promise as a means to identify potential immunosuppressive compounds and to generate hypotheses on potential modes and mechanisms of immunotoxicity [107]. The current and future uses of genomics and proteomics techniques by immunotoxicologists are discussed in chapter 6.

CONCLUSION

In this brief survey we have tried to convey a sense of the dynamic nature of immunotoxicology, a discipline that continues to evolve and incorporate new concepts and techniques while remaining true to its core premise: to evaluate the effect of chemicals and other agents on the structure and function of the immune system. We have explored some of the main inflection points along this evolution including the establishment of a structured testing approach (the tier), the establishment of regulatory guidelines that transformed immunotoxicology from a basic science only to a powerful tool to assess the safety of new drugs and other products, the refinement of approaches to the point when true standardization and validation could occur, and a glimpse into the future of the discipline. Immunotoxicology will no doubt continue to change, but doubtless the basic structure will remain solid for the next 30 years and beyond.

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10 Chapter 10. Opioid-Induced Immunomodulation

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12 Chapter 12. Lead Immunotoxicity

Mouse KlgE 38 µg/dL 12 µg/dL ~5µg/dL 34 41

Rat LDTH (persistent effect assessed 13 weeks postexposure) >112 µg/dL (measured at birth for persistent effect) – 34 µg/dL 33 46–48

Mouse LDTH 87 µg/dL 29 µg/dL – 44 50

Rat KTNF - α (persistent effect assessed 13 weeks postexposure) >112 µg/dL (measured at birth for persistent effect) – 8 µg/dL 33 49

*Lowest BLL Reported With Effect Sensitivity of the immune system to Pb appears to differ across life stages, and

studies in rodents suggest that the gestational and neonatal periods are the most sen

sitive. Compared to adults, the increased dose sensitivity of the embryo-fetus would

appear to fall in the range of 3-12X depending upon the immune endpoint considered.

Recent studies have suggested that exposure of embryos to Pb producing neonatal BLLs

below 10 µg/dL can also produce later-life immunotoxicity (Table 12.2). Furthermore,

FIGURE 12.1 Key alterations of the immune system associated with exposure to Pb.

Skewing of the immune response by lead can alter the risk of disease in the absence of

profound loss of immunocytes.

immunotoxicity persists long after any evidence of prior embryonic Pb exposure. This

latter observation from several laboratories may have implications for the design of

human studies.

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15 Chapter 15. Mechanisms by Which Ultraviolet Radiation, a Ubiquitous Environmental Toxin, Suppresses the Immune Response

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19 Chapter 19. Immune System Ontogeny and Developmental Immunotoxicology

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TABLE 25.3

Summary of Research on Specific Environmental Exposures and Autoimmune

Diseases

Exposure Summary of Current Evidence

Infectious

agents Strong mechanistic evidence from rodent models of autoimmune disease of viral or other infectious agents affecting autoimmunity or progression to overt disease, but harder to demonstrate in humans. Enterovirus (Coxsackie virus) focus of epidemiologic studies in type 1 diabetes, Epstein-Barr virus focus of epidemiologic studies in

multiple sclerosis and systemic lupus erythematosus.

Silica Many epidemiologic studies of scleroderma, lupus, rheumatoid arthritis with fairly consistent and strong associations seen; adjuvant- pro-inflammatory properties. Limited mechanistic research in MRL +/+ lupus mice

Solvents Several epidemiologic studies of scleroderma, undifferentiated connective tissue disease, and multiple sclerosis suggest modest associations with “any” solvents or with organic or chlorinated solvents; Trichloroethylene, paint removers, and mineral spirits are some of the specific solvents implicated in these studies. Mechanistic research in MRL +/+ lupus mice.

Pesticides Few epidemiologic studies of pesticide use in general, or specific pesticides, in relation to any autoimmune disease. Mechanistic research primarily for hexachlorobenzene and malathion. Mechanisms other than endocrine-disruption should be considered, even for pesticides with endocrine-disrupting properties.

Ultraviolet

radiation Positive association with frequency of dermatomyositis in one study; inverse association with risk of diabetes and MS. Inhibition of disease in rodent models of multiple sclerosis, type 1 diabetes and inflammatory bowel disease but acceleration of disease in lupus-prone mice.

Tobacco Different effects seen among diseases; increased risk seen in hyperthyroidism, rheumatoid arthritis, and Crohn’s disease but reduced risks seen in ulcerative colitis and possibly adult-onset type 1 diabetes. Limited mechanistic research.

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