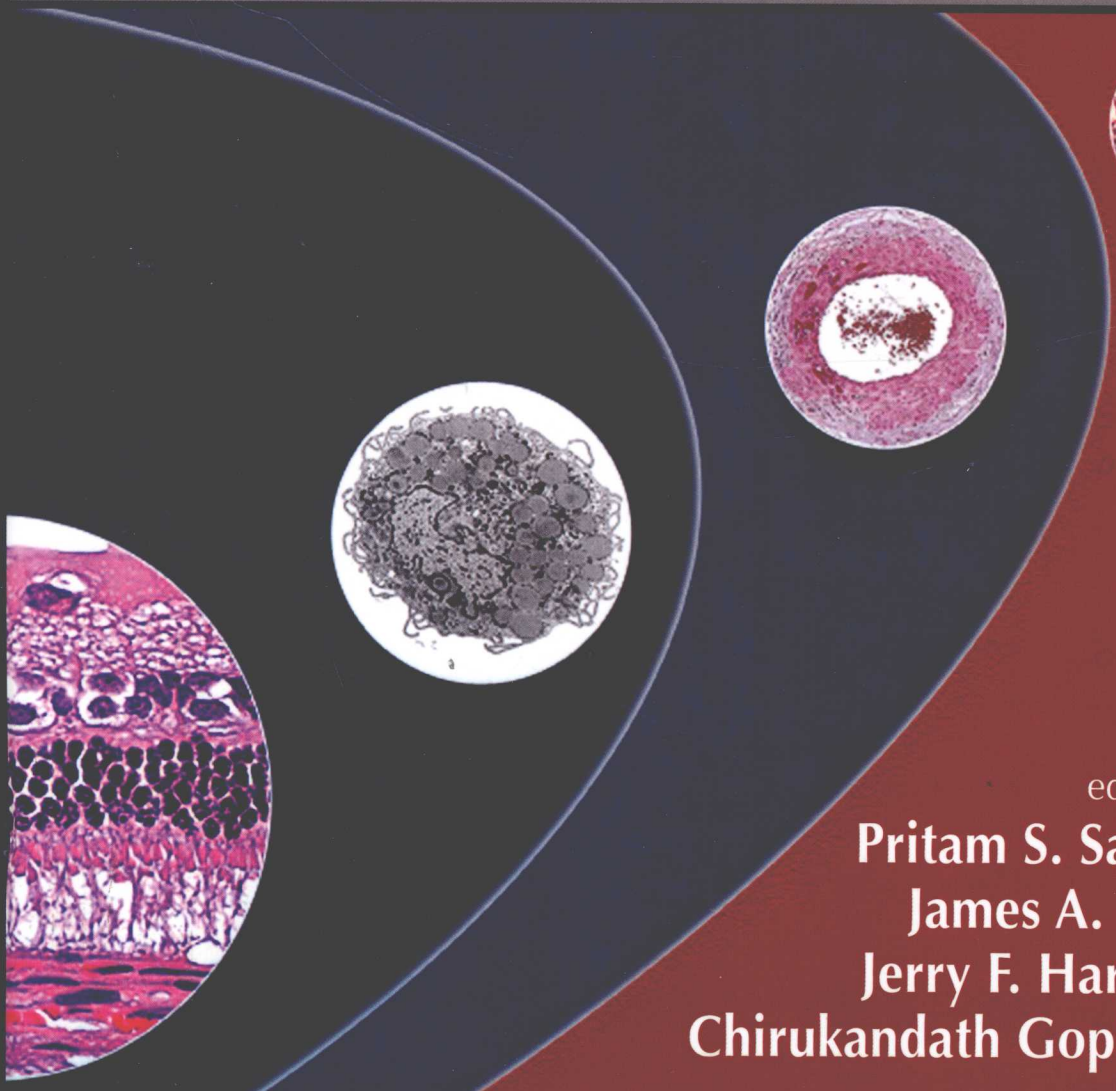
TOXICOLOGIC PATHOLOGY

NONCLINICAL SAFETY ASSESSMENT



edited by
Pritam S. Sahota
James A. Popp
Jerry F. Hardisty
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Preface

Toxicologic Pathology: Nonclinical Safety Assessment is the result of careful planning and diligence by the editors and authors. When entering the field of toxicologic pathology related to drug development, the authors recognize the currently limited and scattered resources available to assist the toxicologic pathologist, despite the best of basic diagnostic training and committed mentorship. The editors have each served as mentors to toxicologic pathologists entering the arena of drug development over the years and were struck by these shortcomings. Therefore, the current text has been specifically designed to assist the students/residents and toxicologic pathologists in the early phase of their careers by serving as a resource that can effectively be used as a ready reference next to the microscope. Of course, even the most experienced pathologist in drug development has not "seen it all," as areas of drug emphasis shift over time and more targeted therapies are developed, resulting in previously unseen, exaggerated pharmacologic or off-target effects. Since the initiation of this book, toxicologists have expressed great interest in such a resource to better appreciate the gravity of pathological lesions and processes described by the pathologist in toxicology reports and to promote a much more fruitful dialog with pathologists toward a common understanding.

Toward these ends, the editors have organized this volume into two major sections, each composed of multiple chapters. Since it is critical that the toxicologic pathologist has a basic understanding of areas beyond diagnostic pathology to function effectively in an ever-increasing, integrated approach to drug development, eight concept chapters are included. While numerous concept chapters are possible, the current book includes those eight topics that have been judiciously selected to orient the pathologist in areas that are important for effective interaction with other pathologists as well as the many nonpathologists involved in drug development. The second major section is composed of 13 chapters oriented by organ system. While this approach is generally used in pathology texts, the limitation of presenting material on a multiorgan pathologic entity (e.g., phospholipidosis) presented across several chapters is recognized. In such instances, information in various sections should be identifiable from the index.

Any book of this nature is only as good as the authors who prepare the specific sections, thus their selection was given very careful consideration. They were obviously chosen for their knowledge, expertise, and focused interest on a topic. While multiple potential authors may be able to develop a solid treatise on a topic based on literature review, we also know that extensive knowledge and expertise based on the experience of working through toxicologic pathology issues that often do not appear in the literature add a critical dimension. Therefore, the book was designed to present important information, both published and unpublished, as gained through personal experience, so this knowledge can be used by others to improve the quality of drug safety evaluation and, as importantly, to expedite and improve the efficiency of the process. The editors and the future readers are indebted to the authors for sharing such personal knowledge in addition to organizing and summarizing the latest information available in the literature.

While extensive care has been taken by the authors to identify the most important topics and effectively address them within the constraints of this book, there will inevitably be topics that have been missed or have not been given enough space, and there will certainly be unforeseen topics that will need to be added in the future. Therefore, the editors solicit input from readers as they use the text. The goal is to continually upgrade and update the book at reasonable intervals so it can be of even greater value to future users. Creators and users of future revisions will surely benefit from the contributions made by the readers and users of this initial edition of *Toxicologic Pathology: Nonclinical Safety Assessment.*

Acknowledgments

The editors wish to acknowledge and thank the many individuals who made valuable contributions toward the completion of this book. Their efforts not only ensured the quality of the text and photographs but also contributed to its timely completion.

We acknowledge Robert H. Spaet for reviewing each chapter in detail for consistency, completeness, and overall harmonization. His contributions are especially appreciated as they come from the viewpoint of a bench toxicologic pathologist, the individual for whom this book is primarily written. Robert has over 35 years of experience as a toxicologic pathologist in the pharmaceutical industry. He has also served as an international project team representative for a number of successfully marketed pharmaceuticals. This level of experience in toxicologic and regulatory pathology and an appreciation for the questions that are most often asked by the bench toxicologic pathologist made him the perfect individual to review this work to keep it focused on the needs of the prospective reader and thereby ensure its use as a practical reference next to the microscope.

We would like to thank Gregory Argentieri and Diane Gunson for their contributions toward the postprocessing of images, photocomposition, photo layout, and review of the chapter figures and legends. We appreciate their willingness to devote considerable expertise and time to this project as it was only after long hours of such dedication that it was successfully completed. We would also like to thank Gregory Argentieri and David Sabio for helping create the cover of this book. In addition, we express our gratitude to Cathy Cummins for reformatting the text and references before submitting the final drafts of all chapters to the publisher and to Robert Stull for spot verification of literature references as a quality control check.

The editors also wish to acknowledge those individuals who provided additional scientific review of selected chapters: David Beckman, Philip Bentley, Dominique Brees, Kristin Henson, Daher Ibrahim Aibo, William Kluwe, Vito Sasseville, and Spencer Tripp. We also want to thank Page Bouchard for his continued support that helped us to achieve the highest-quality input and optimum timelines for submission of the final draft to the publisher.

Lastly, the editors wish to acknowledge the excellent working relationship with the Taylor & Francis staff, especially Jill Jurgensen, Sara Svendsen, Sharlene Glassman, Amor Nanas, Ed Curtis and Barbara Norwitz, that resulted in expert advice and timely responses to their many inquiries.

Editors

Pritam S. Sahota, Novartis, East Hanover, New Jersey, has extensive experience in toxicologic pathology and drug development within the framework of nonclinical safety assessment of pharmaceuticals and is Executive Director, Preclinical Safety, at Novartis Pharmaceuticals. Dr. Sahota obtained his veterinary medicine (BVSc) and veterinary pathology degrees (MSc and PhD under Dr. Balwant Singh) from Punjab Agricultural University, India. He is a Diplomate of the American Board of Toxicology.

After receiving his PhD, Dr. Sahota emigrated to the United States in 1976 and began working as a toxicologic pathologist for Dawson Research Corporation (DRC) in Orlando, Florida, a contract research organization involved in the preclinical safety evaluation of drugs and chemicals. Under the leadership of Dr. Thomas E. Murchison, he accepted roles of increasing responsibility over the next 10 years. As scientific director, he was responsible for the scientific aspects of pathology and toxicology at DRC. While working briefly for Dynamac Corporation in North Carolina, Dr. Sahota conducted retrospective scientific audits of over 20 NTP rodent carcinogenicity studies and participated in discussions with the representatives of NTP, FDA, and EPA to summarize the results of scientific audits of over 200 carcinogenicity studies. In 1987, Dr. Sahota joined Ciba-Geigy Pharmaceuticals in New Jersey as head of pathologists in preclinical safety and was responsible for establishing pathology peer review and quality control systems. He continued to work primarily in this position with increasing responsibility at Ciba-Geigy and then Novartis (Ciba/Sandoz merger in 1997) to become director and eventually executive director of pathology. During this time, he also served as an international project team representative for a number of successfully marketed CNS, immunosuppression, diabetes, and cardiovascular drugs, including Diovan, a widely used antihypertensive.

Dr. Sahota additionally held an adjunct academic appointment at the University of Medicine and Dentistry, New Jersey, for 8 years. Recently, he has successfully led the global preclinical safety initiatives at Novartis, including patient centricity (patient in the lab), review of best practices in cardiotoxicity and ocular toxicity safety assessment, and evaluation of rodent carcinogenicity potential based on noncarcinogenicity studies to minimize future delays in regulatory submissions.

James A. Popp, Stratoxon LLC, Lancaster, Pennsylvania, is widely recognized for his research and leadership contributions in toxicologic pathology and toxicology with special emphasis on nonclinical safety assessment of pharmaceuticals. He is an independent consultant at Stratoxon LLC. Dr. Popp received a doctor of veterinary medicine followed by a PhD in comparative pathology and is a Diplomate of the American College of Veterinary Pathologists. Following postdoctoral training in biochemical pathology and chemical carcinogenesis, he served on the faculty of the Division of Comparative Pathology in the College of Veterinary Medicine and Department of Pathology in the College of Medicine at the University of Florida before joining the Chemical Industry Institute of Toxicology (CIIT) shortly after the institute was founded. Over the ensuing 15 years, Dr. Popp developed and directed a productive research program in hepatotoxicity and hepatocarcinogenesis with emphasis on liver tumor promotion using stereologic approaches for assessing morphological development of tumors. During part of his tenure at CIIT, he served as a department head of the Department of Experimental Pathology and Toxicology and vice president of the institute. He has held several vice president positions overseeing safety assessment programs in the pharmaceutical industry for 11 years before initiating consulting activities in safety assessment at Stratoxon LLC.

Dr. Popp has served in the leadership of several professional societies including the positions of president of the Society of Toxicologic Pathology, president of the Academy of Toxicological

Sciences, and president of the Society of Toxicology. Dr. Popp has been a frequent contributor to governmental toxicologic pathology and toxicology efforts including participation in numerous pathology working groups at the National Toxicology Program (NTP). He has completed a 3-year term on the NTP Board of Scientific Counselors and the report on carcinogens subcommittee. Dr. Popp has also served as chair of NTP special workshops and served as chair of the board of scientific advisors for the FDA National Center for Toxicological Research.

Jerry F. Hardisty, Experimental Pathology Laboratories, Sterling, Virginia, has extensive expertise in nonclinical safety assessment of pharmaceuticals through his direct microscopic evaluation of tissues and contribution to resolution of toxicologic pathology issues related to drug development. He is the CEO and President of Experimental Pathology Laboratories, Inc. (EPL). He graduated from Iowa State University College of Veterinary Medicine and received his pathology training in the US Army Preceptorship Program. He has been a Diplomate of the American College of Veterinary Pathologists since 1976.

Dr. Hardisty is an adjunct assistant professor with the North Carolina State University College of Veterinary Medicine. He has worked with the NCI/NTP Carcinogenesis Testing Program closely for over 25 years. He has participated in the publication and presentation of significant results of the NCI/NTP Pathology Quality Assessment Program and of several specific carcinogenesis bioassay tests. He has coauthored several publications in experimental pathology, pathology quality assessment, and pathology peer review.

Dr. Hardisty has served on the editorial board for Toxicologic Sciences, Toxicologic Pathology, and Experimental and Toxicologic Pathology. He specializes in the conduct of Pathology Peer Review of subchronic and carcinogenicity nonclinical toxicology studies. Dr. Hardisty also organizes and chairs pathology working groups and scientific advisory panels in the United States, Japan, and Europe. He is active in the Society of Toxicologic Pathologists (STP) as a member of the Executive Committee, Standard Systematized Nomenclature and Diagnostic Criteria Committee (SSNDC), liaison with the American College of Toxicology, and as president (2001–2002). He has also served as the chair of the STP nominating and fundraising committees. He is a member of the International Academy of Toxicologic Pathologists and served as the North American director of the IATP.

Chirukandath Gopinath, Alconbury, Cambridgeshire, UK, has expertise in toxicologic pathology related to safety assessment of pharmaceuticals based on a distinguished career as a bench pathologist, supervisor of other toxicologic pathologists, and author of publications relevant to drug development. He is an independent consultant in toxicological pathology in the United Kingdom. He has worked as director of pathology at Huntingdon Research Center, Cambridgeshire, UK. His other work positions include head of pathology at Organon International, the Netherlands; Lecturer at the Department of Veterinary Pathology, University of Liverpool, UK; Veterinary Officer, British Guyana; lecturer of veterinary pathology, University of Kerala, India; and veterinary surgeon, Kerala, India.

Dr. Gopinath received his veterinary degree from the University of Kerala, India, and did his postgraduate training at the University of Liverpool, UK, where he obtained his master's and PhD. He gained his membership with the Royal College of Pathologists, London, in 1977 and was awarded an honorary fellowship of the International Academy of Toxicological Pathologists in 2004. Dr. Gopinath has held several positions in various professional societies including past president of BSTP and IFSTP. He has published extensively in scientific journals and many books on toxicological pathology. Dr. Gopinath has organized and operated several educational modules on the topics of toxicological pathology in different countries including India, China, and Brazil.

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Section I

Concepts in Drug Development

1 Overview of Drug Development

James A. Popp and Jeffery A. Engelhardt

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1.1 SCIENTIFIC HISTORY

1.1.1 Origin of Modern Therapeutic Agents

As with all other endeavors in human progress, the identification and use of therapeutic agents to treat disease and alleviate pain and suffering have changed dramatically over time (Rubin 2007; Scheindlin 2001; Tsinopoulos and McCarthy 2002). The origin of the use of potential therapeutic agents is lost in antiquity but certainly dates back several millennia. The use of presumed therapeutic agents was described in written records from ancient Greece and Egypt, as well as other areas of the world. While a detailed history of drug discovery of pharmacologic agents is available (Sneader 2005), only a brief overview is provided here.

As might be expected, the origin of the use of various agents for therapy apparently began through trial and error, though probably influenced by significant levels of superstition. From ancient times

until the nineteenth century, agents of reputed therapeutic value were primarily, although not exclusively, "botanicals" but also included selected metals and, in some cases, various animal parts. The collection of various plant materials including leaves and roots provided the primary resources of the "pharmacy" for several millennia. To enhance the possibility of therapeutic success, concoctions made from several dozen sources were sometimes prepared, providing an early approach to "polypharmacy." While some material had varying therapeutic value, the specter of toxicity stalked the use of these agents. In the highly developed world of today, the use of relatively crude botanical products in native, dried, or extracted form has been largely supplanted by much purer products made by synthetic processes. While we may at first think of botanical products as being associated with less developed cultures, it is important to recognize that the use of botanicals has continued to this day for marketed drugs, an example being the senna-based laxatives that are currently on the market. Indeed, in the last several decades, we have seen a resurgence of the use of many crude plant-based agents with reputed therapeutic effects, which have been collectively referred to as herbal products or "nutraceuticals." It is important to note that these products do not fall under the review of the Food and Drug Administration (FDA) in the United States as long as no therapeutic claim is made. However, anyone can peruse the local drugstore or "natural products" store and find innumerable products that appear to be making therapeutic claims. These agents have generally not been subjected to modern toxicological evaluation and, in most cases, not subjected to even rudimentary toxicity testing. Toxicologic pathologists rarely see the results of these products unless they participate in government programs such as the National Toxicology Program.

The identification of the action of naturally derived agents such as curare that was used in poison arrows, and the subsequent study of the action of chloroform in the latter half of the nineteenth century, set the basis for the future of pharmacology. In the later part of the nineteenth century and the early decades of the twentieth century, the population of the Western world became more health conscious and interested in disease remediation. This led to the rather bleak period of "patent medicines" where numerous manufacturers produced a wide assortment of products for sale with wide disease prevention and disease curative claims. It should be noted that patent medicines during this era do not suggest that they were legally patented as occurs under current legal processes. Indeed, "patent medicines" in the earlier era were not legally patented. These products were widely marketed through extensive advertising campaigns using print medium. Claims for cures ranged from the improvement of normal bodily functions to a cure for cancer; most impressively, or perhaps unimpressively, diverse curative capacities were claimed for a single product. During this period, there was no regulatory control over claims of either efficacy or toxicity, with the United States lagging several other Western countries in developing a modicum of control. As one can well imagine, the efficacy claims could not be substantiated. On the basis of knowledge of the ingredients, it is apparent today that they would have most likely not had any therapeutic value. While the use of these products undoubtedly prevented or delayed the patient's efforts to seek medical attention for real medical conditions, an equal if not greater issue was the fact that a number of these products were toxic. Multiple incidences of life-threatening toxicity occurred in adults as well as in children, either through the administration of toxic "medicines" of the day or through adulterated foods. The attention to these issues through the effort of government officials such as Harvey Wiley and a newly interested press resulted in the first laws addressing the safety of foods and drugs, which occurred in the first decade of the twentieth century. This effort provided a basis for a very nascent activity to evaluate safety, and later efficacy, although progress on this front was relatively slow.

Giant strides toward the scientific development of therapeutic agents occurred in the middle of the twentieth century with the advent of what some have referred to as the antibiotic era (Tsinopoulos and McCarthy 2002). Along with the identification of the first sulfa drugs, the identification of penicillin in 1928 was a landmark event resulting from an interesting combination of serendipity, careful scientific observation, and pursuit of the scientific process. The use of these new antibiotics, after the development of production techniques, resulted in a dramatic change in survival of battlefield combatants in World War II, setting the basis for wider acceptance and use throughout the general