Pathologists, investigators, and regulators have long recognized the important role of clinical pathology in the holistic assessment of pathophysiologic, toxicologic, and pharmacologic effects in preclinical safety studies. However, in the current era of safety assessment, a redefinition of the practice of clinical pathology is long overdue. By virtue of the quantitative nature of the results, interpretation of clinical pathology data can appear deceptively simple: it is only a matter of collecting the same basic hematology and clinical chemistry panels, comparing control data to identify the effects, then using predefined, thresholds applied in the same way to every study to determine test article effects and adversity. Easy enough, right? If any preconceived notions about toxicologic clinical pathology need updating (or expanding), we hope this special edition of Toxicologic Pathology focused on contemporary clinical pathology perspectives goes a long way toward accomplishing this goal.

Toxicologic clinical pathology is a multifaceted discipline focused on applying a diverse set of analytical methods to identify and characterize toxicopathologic effects. The wide array of end points and analytical platforms has steadily grown in number and complexity over the last decade. As there is continued demand for improved safety monitoring, risk–benefit analysis, and translational strategies, we expect these trends to continue. Some clinical pathology end points provide the most relevant measure of a drug effect, for example, hematology parameters such as red blood cell or platelet count. Other end points serve as indicators of target organ injury, for example, increased circulating transaminase activities due to hepatic injury. While other parameters permit characterization of secondary, or indirect effects, such as electrolyte loss in animals that are vomiting due to gastrointestinal injury. Because clinical pathology tests are noninvasive, generally standardized from laboratory to laboratory, and often not species-specific, most clinical pathology end points are highly valuable in the translation of nonclinical toxicology to clinical safety monitoring.

Modern clinical pathology is much more than hematology, coagulation, and clinical chemistry testing—it is a biomarker science. There are acknowledged gaps in safety monitoring for various organ toxicities and as the biopharmaceutical and regulatory landscape has evolved, private–public partnerships have formed to promote the discovery and evaluation of new safety biomarkers. Clinical pathology is integrative and systems biology. An understanding of how organ toxicity can have direct and indirect manifestations is key to the accurate interpretation of laboratory data. Clinical pathology is a bioanalytical science. Experimental study design, sample collection and processing, and the analytical method all affect the measured value and ultimately the quality and interpretation of the data. The discipline of clinical pathology has expanded to play a key role in each of these scientific areas which are now fundamental components of contemporary safety assessment practices.

In recent years, Toxicologic Pathology has addressed best practices for clinical pathology (Tomlinson et al. 2013) in general toxicology, and in specific experimental settings such as pharmaceutical recovery (Tomlinson et al. 2016), carcinogenicity (Young et al. 2011), and minipig (Stricker-Krongrad et al. 2016) studies. In addition, the journal has captured evolving trends in clinical pathology through symposia summaries (Jordan et al. 2014; Everds 2015). This special issue of Toxicologic Pathology is the first to focus entirely on the field of toxicologic clinical pathology. These diverse articles by industry leaders describe new and emerging technologies, applications of clinical pathology in nonclinical research, nonclinical to clinical translation of clinical pathology end points, and contemporary perspectives on interpretation of clinical pathology results.

The discovery of noninvasive, predictive, and translational means of detecting organ injury continues to be the “holy grail” for biomarker development scientists. Nowhere is this notion truer than for detection of pancreatic and gastrointestinal injury. Traditional biomarkers of pancreatic injury have been
unreliable, for example, measurement of serum amylase and/or lipase activities, both of which lack the sensitivity and specificity to accurately identify test article–related effects in the pancreas (Rakonczay et al. 2008; Usborne et al. 2014). As the exploration of microRNAs (miRNAs) as useful preclinical and translational biomarkers continues, several promising miRNA candidates have been described in the context of acute drug-induced pancreatic toxicity (Wang et al. 2016). Similarly, biomarkers utilized to detect gastric and/or intestinal injury have been limited (e.g., gastrin, citrulline) and generally have characteristics that discourage their widespread application (John-Baptiste et al. 2012). Presented here are several premonitory biomarkers that have demonstrated the ability to detect drug-induced gastric (serum pepsinogen I) and intestinal (serum and fecal miRNAs) injury (Enmulat et al. 2016; Kalabat et al. 2016).

Also included in this edition, are several papers that provide greater insight into the practical application of new and established clinical pathology tests in the nonclinical setting. Cardiac troponins have been qualified by the Food and Drug Administration as translatable biomarkers in the rat and dog to indicate drug-induced structural damage of the heart (Hausner et al. 2013). At the time of this qualification, there was insufficient information on the use of cardiac troponins in nonhuman primates on which to base a recommendation. Since then, there has been a steady stream of publications evaluating cardiac troponins in this species, including a thorough understanding of the preanalytical variables that may affect the measured values (Reagan et al. 2016). Natriuretic peptides are valuable biomarkers of cardiac hypertrophy and ventricular stress in humans and animals. An elegant study by Dunn et al. (2016) demonstrates the utility of these biomarkers to identify drug-induced, maladaptive cardiac hypertrophy in the rat. Although bone marrow cytological examination is an established technique in laboratory animals, published information on the background findings in nonhuman primates is more limited than in other species. The contribution by Carter, Cregar, and Aulbach (2016) provides an updated and comprehensive assessment of normal bone marrow cytology in the nonhuman primate, further expanding the reference literature for nonclinical toxicity studies. Finally, we have a case example of the mechanistic workup and evidence-based risk assessment of an unusual clinical pathology finding—drug-induced green discoloration of the serum (Diaz et al. 2016).

Assessment of clinical pathology data without a clear understanding of the sources of analytical, biological, and procedure-related variability can result in inaccurate, misleading, or blatantly incorrect conclusions. This special issue of Toxicologic Pathology is fortunate to include the collective expertise of a number of subject matter experts specifically addressing variability commonly observed in clinical pathology data generated in preclinical safety studies. A discussion of the important role of preanalytical variables on clinical pathology data, such as diet, animal handling and restraint, experimental procedures, and sample handling, emphasizes the need to be familiar with all study processes in order to provide accurate data interpretation (Eversd 2016). A review of the influence of study design variables on the generation and interpretation of clinical pathology results (Aulbach 2016) also highlights the importance mitigating study design elements that limit the interpretive value of the clinical pathology data. Through unique case examples, Schultze and Irizarry (2016) illustrate the potential impact of analytical errors on clinical pathology data and strategies to avoid these pitfalls. Taken together, these contributions provide comprehensive recommendations and valuable references that will help readers recognize and limit testing errors and variability among clinical pathology data in preclinical animal studies.

Crafting a high-quality clinical pathology report depends not only on the acquisition of accurate data but also on the consistent, careful review and synthesis of all pertinent experimental information. In this issue, one of the foremost leaders in the field of toxicologic clinical pathology, Robert (Bob) Hall, shares his unique and practical insights on clinical pathology data interpretation and reporting. While a methodical, thorough approach is important, the uniqueness of each study also requires flexibility and practical understanding. Bob provides a pragmatic overview of the reporting process and discusses some of the potential pitfalls, such as overreliance on statistical tools and reference intervals/historical ranges (Hall 2016).

Characterizing adversity of xenobiotic effects is one of the most critical objectives of animal safety studies. This topic has been recently discussed within the anatomic pathology community (Kerlin et al. 2016; Palazzi et al. 2016), and in this issue, Ramaiah (2017) establishes important principles for characterizing adversity in toxicologic clinical pathology assessment. Notably, few clinical pathology end points are adverse in and of themselves, but more often, reflect an overall pathologic or physiologic alteration. In most cases, a designation of adversity or nonadversity based on individual clinical pathology effects alone is not appropriate. Key elements for consideration in adversity for clinical pathology end points include the use of a weight-of-evidence approach, consideration of pathogenesis, and rapidity of onset and persistence of findings with repeated dosing.

In summary, this issue of Toxicologic Pathology provides an exciting first look at several newly emerging protein and miRNA biomarkers used to characterize gastrointestinal and exocrine pancreatic toxicity, areas that have traditionally lacked sensitive and specific noninvasive indicators of injury. In addition, updates to the use of several established cardiovascular and hematologic biomarkers are described, further highlighting the value and potential limitations of such end points. Several articles provide readers a contemporary update on several important areas of focus when reviewing and interpreting clinical pathology data from toxicology studies including sources of variability and strategies to limit these influences. And lastly, an important perspective on the role of clinical pathology effects in the determination of adversity is presented. We hope the collective works presented in this issue will be of interest to all scientists and researchers involved in the conduct and review of data from preclinical toxicology studies providing a fresh perspective on the ever-evolving field of clinical pathology.
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