Toxicologic pathologists have been involved in drug and agricultural chemical development and safety assessment of xenobiotics for several decades. In 1971, President Nixon’s declaration of “War on Cancer” resulted in a marked expansion of the National Cancer Institute (NCI) Bioassay Program. Starting then and continuing to the present time, there has been an increasing involvement of government, industry, and private sector toxicologic pathologists in the evaluation and interpretation of animal bioassay data. The role of the toxicologic pathologist has traditionally involved diagnosis of hematoxylin and eosin–stained tissue sections and integration and interpretation of in-life data, clinical pathology data, and necropsy findings with the lesion incidences at the conclusion of each study. (Apologies to my clinical pathology colleagues for focusing on anatomic pathology in this opinion piece.) Initial emphasis has been on cancer, with a more recent focus on noncancer endpoints including immunotoxicity, neurotoxicity, and reproductive toxicity. From the very beginning of the NCI Bioassay Program in 1962 (Page 1977) to the present time, there has been a continual search for alternatives to the rodent cancer bioassay.

This is prompted by the high cost of the resource-intensive rodent bioassay, the questionable relevance of some findings in a rodent study to human health risk, and the large number of chemicals in commerce and in the environment without adequate toxicity data. In the pharmaceutical industry, the same questions of costs and relevance apply to rodent and other test species, plus a desire to shorten the interval from drug discovery to relevant clinical trials. A major issue for the pharmaceutical firms is the inability of rodent studies to predict the rare but often serious hepatotoxicity that results in dropping a compound when it is in clinical trials or, worse, when the compound is already on the market (Watkins 2005; Lee and Senior 2005; Watkins et al. 2011).
Over the past decades, a variety of short-term animal model alternatives to the conventional chronic rodent bioassays have been proposed, each accompanied by considerable hand waving and promising to be the philosopher’s stone to definitively identify toxicities and human carcinogens. The 6-month strain-A mouse lung tumor bioassay was proposed as a carcinogen-screening test in 1969 and in the 1970s (Shimkin et al. 1969; Stoner et al. 1973; Stoner, Weisburger, and Shimkin 1975; Theiss et al. 1977). Other shorter-term animal studies, some with international input, have been proposed over the years and include some variations of rodent liver focus assays (Maronpot, Pitot, and Peraino 1989; Shirai 1997). Capitalizing on the identification of the role of oncogenes in carcinogenesis, gene manipulation technology allowed the development of genetically engineered mice and the proposal that a 6-month cancer bioassay in these transgenic mice would more quickly identify agents that were carcinogenic while using fewer animals (Pritchard et al. 2003). The use of genetically engineered mice in cancer bioassays has not fulfilled the desire to replace the conventional rodent cancer bioassay, especially for testing of agrochemicals and environmental agents. Recent emphasis on noncancer endpoints has led to other alternative tests such as the rat uterotrophic assay for endocrine disruptors (Tyl et al. 2010). Most of these alternative test systems involve animal exposures and rely on the expertise of the toxicologic pathologist for assessment and interpretation. Although not replacing the traditional bioassays, all have provided tangible contributions to basic research and understanding of carcinogenesis and represent useful tools for hypothesis-driven research questions.

Other historical and contemporary alternatives for diagnosis, identification, and assessment of toxicity and cancer have emerged over the past few decades. In the mid- to late-1960s, there was considerable fanfare about a new carcinoembryonic assay to detect early colon cancer, which was subsequently shown to lack the specificity and sensitivity of initial predictions, and although not as heavily used these days, it is sometimes useful to monitor the progress of colon and other cancers (Cohen 2004b). New approaches to the animal-testing paradigm received considerable attention in the 1970s with promotion of bacterial (Ames, Durston, et al. 1973; Ames, Lee, et al. 1973) and other genotoxicity testing schemes, which are performed as a testing battery. The implied promise was that genotoxicity batteries would clearly identify agents with carcinogenic potential. Over subsequent years, various components of the genotoxicity testing battery have fallen out of favor, and new tests have been proposed. Genotoxicity is a decision tool and regulatory requirement that is still used today, especially for setting priorities and categorizing xenobiotics, but it is recognized as not being sufficient enough to preclude further animal studies. Immunologic markers as tools for diagnosis and assessment of toxicity endpoints enjoyed initial popularity in the 1970s, and although various markers including immunohistochemistry are clearly contributory and part of the pathologist’s toolbox today, these alternative strategies have not fulfilled all initial expectations and suffer from lack of universal standardization (Dunstan et al. 2011).

In the 1980s and 1990s, identification of mutations in proto-oncogenes and tumor suppressor genes was in vogue. Identification of these genomic alterations is clearly contributory to our understanding of carcinogenesis, and they definitely represent risk factors for specific cancers. However, any hope that oncogene mutational profiles would predict positive rodent bioassay responses has not been realized. There is some contemporary effort retrospectively using mutational profiles to classify specific rodent bioassay cancer responses as similar to human cancers versus responses that are most probably rodent specific (Hoenerhoff et al. 2009; Honerhoff et al. 2011; Pandiri et al. 2011). The oncogene era has been followed more recently with the “omics” revolution (transcriptomics, proteomics, and metabolomics), with the promise that a genomic profile combined with computational and physiological dynamic modeling plus some clever database mining will provide a potential departure from heavy dependence on costly animal studies (Waters and Fostel 2004; Waters, Jackson, and Lea 2010). Still more recently, robotic high-throughput screening promises to identify critical toxicity pathways and networks to classify potentially toxic agents and set priorities for more in-depth follow-up studies (Schmidt 2009; Judson et al. 2011; Krewski et al. 2011).

Let there be no doubt, I firmly believe the various technologies that have emerged and captivated the scientific and lay communities are tremendously valuable tools for understanding basic pathobiology and have meaningful application in clinical medicine. However, they have fallen short on expectations prompted by the euphoria that accompanied their initial introduction. What has accompanied the more recent genetic, computational, molecular, and high-throughput screening approaches has been the generation of a large number of molecular biologists as participants in identifying toxicity and carcinogenic potential. Simultaneously, there has been some blurring and less apparent role for the toxicologic pathologist in the present postgenomic era.

Our relentless desire to overcome the shortcomings of the conventional 2-year rodent cancer bioassay continues. Two recent approaches to mitigate or even eliminate the need for the 2-year rodent bioassay have been proposed. Both are based on a 40-year history of conducting 2-year rodent cancer studies and the generation of a robust database plus an appreciation of critical elements in the carcinogenesis process. One approach is to modify the rodent short-term 90-day or 6-month study traditionally used to establish the maximum tolerated dose for the 2-year cancer bioassay. By adding some potential to measure cytotoxicity in a 90-day or 6-month study together with information regarding agent genotoxicity, structural alerts, and hormonal activity, a decision-tree approach has been proposed to replace the conventional 2-year rodent bioassay (Cohen 2004a). This would be most applicable to chemicals in commerce and in the environment. The second approach is similar, involves drug development, and is based on data analysis from the pharmaceutical industry (Sistare et al. 2011). This approach
proposes that identification of histopathological risk factors for rat neoplasia from a 6-month rat toxicity study together with genotoxicity results, evidence of hormonal perturbation, and a 6-month cancer bioassay in genetically engineered mice is sufficient to eliminate the need for a 2-year rat cancer bioassay in drug development. These two recent alternatives to conventional 2-year rodent animal studies will successfully engage the skills of the safety assessment toxicologic pathologist, simultaneous allow characterization of potential target organ toxicity, and potentially may reduce the number of 2-year rodent cancer studies. Anticipated modifications of these toxicity studies to include developmental neurotoxicity, immunotoxicity, and reproductive toxicity plus efforts to make the art of pathology more quantitative will further require a participatory role for safety assessment toxicologic pathologists.

This brings us to the basic question as to what role the safety assessment toxicologic pathologist will play in the 21st-century postgenomic era. While there is a definitive diagnostic and interpretative role for the toxicologic pathologist in the proposed rodent toxicity and genetically modified mouse studies, what role will the toxicologic pathologist fill in the alternative approaches involving molecular biology, high-throughput screening, and whatever the next initiative will bring to the table? The prospect that the toxicologic pathologist might also become a closet molecular biologist should not be considered lightly. The rate of advances in molecular biology and associated in vitro techniques is such that one must remain fully engaged on a daily basis to be a cutting-edge relevant participant on the molecular biology scene. For most of us, that degree of commitment would compromise the ability to maintain expertise in tissue diagnostic pathology. Since it is not reasonable to expect a molecular biologist to render adequate tissue lesion diagnoses, there will be a continued need for expert toxicologic pathologist practitioners. But to be a relevant team participant rather than a diagnostic technician, the toxicologic pathologist will need to acquire a sufficient understanding of molecular and computational techniques to provide informed and useful input into design and interpretation of studies.

By virtue of training and experience, toxicologic pathologists, especially those with a veterinary background, are in an ideal position for bridging the diverse and emerging technologies and linking their input to pathobiology and toxicology. Their perspective will identify synergies to more accurately predict human health consequences. This bridging and synergy building is a logical means for toxicologic pathologists to provide leadership roles in integrating new technologies into the matrix of traditional toxicology. What the toxicologic pathologist brings to the table is a comprehensive understanding of interspecies anatomy, physiology, and disease, thereby providing the phenotypic anchors for the input provided by genomic and in silico endeavors, high-throughput screening, and other technologies. The integration of genomic and computational data with normal and abnormal interactions of the endocrine, lymphoreticular, respiratory, cardiovascular, reproductive, and other tissues is consistent with the contemporary strategy of using a “systems” approach to understanding toxicology. Who better to integrate the diverse organ system interactions with data from new technologies than the toxicologic pathologist?

Another reason for the toxicological pathologist, who is not familiar with the field, to develop an interest in molecular biology is the advent of the new compounds coming on the market that employ molecular technology to target specific pathways in the tumor cells. Thus, many toxicological pathologists find themselves evaluating toxicity induced by a specific kinase or protein. These compounds often induce unusual toxicities not commonly seen with more traditional compounds that are generally more toxic to cancer cells but are often toxic to many other tissues.

Realizing that no one person can know everything, how do we as toxicologic pathologists fulfill a leadership role over the next few decades? The younger toxicologic pathologists, recently out of a training program or residency, already have a reasonable comfort level with contemporary molecular biology but lack historical experience in designing, evaluating, and peer reviewing conventional safety assessment histopathology and evaluating clinical pathology endpoints generated during toxicity studies. It is well known that most residencies as well as training programs focused on acquiring a PhD provide little exposure to toxicologic pathology. On the other hand, traditional toxicologic pathologists, having moved lots of glass slides across the microscope stage or having dealt with group means and outliers in clinical chemistry or hematology for years, may be perplexed when confronted by the fast-changing lexicon of molecular biology and the array of new technologies that threaten to replace their training and experienced-based judgment process. The role for both of these categories of toxicologic pathologist plus any others in academia or research is the same. They need cross-cultural exposure and basic understanding of alternative disciplines to assume a leadership role on any team that sets out to tackle a biomedical problem. They will certainly continue to bring their unique expertise to the table. However, to help validate and successfully integrate the input from the most promising of these technologies with conventionally acceptable toxicity and pathology endpoints, cross-cultural exposure, appreciation, and some level of understanding are necessary.

I am proposing that to be maximally effective in bringing a relevant perspective to bear on safety assessment and toxicity studies, the toxicologic pathologist will need cross-disciplinary exposure. For the more senior bench pathologist, the question is how much of a dose of computational biology, bioinformatics, or the next new technology is necessary to be an effective team member, to provide leadership, and, importantly, to maintain a passion and clear appreciation of the importance of one’s own contribution? The answer to the question depends on the individual’s career choices and objectives. Obviously, one can read slides all day and provide diagnoses to others to interpret and never think about cluster analysis, heat maps, dendograms, oncogene point mutations, or the latest type of RNA. Or, one can get caught up with the fast-evolving...
molecular biology and informatics scene and rarely even turn on a microscope (yikes!). Assuming that neither of these two extremes is appropriate, then some program of ongoing exposure to alternative disciplines is necessary. There is no escape.

In part, cross-disciplinary exposure is already being provided through continuing education (CE) courses at society annual meetings. For the younger toxicologic pathologist with a reasonable understanding of molecular biology and toxicogenomics, the CE exposure will need to emphasize diagnostic and descriptive histopathology courses and include events similar to the NTP Satellite Symposia held at the beginning of each Society of Toxicologic Pathology annual meeting. Even better, perhaps, is the training module program of the British Society of Toxicologic Pathology, where there is presentation and actual slide reading and one gains relevant diagnostic experience with all major organ systems over time. Furthermore, the opportunity to sit at a double-headed microscope with a seasoned veteran toxicologic pathologist and talk through actual histologic material may provide better training. The use of Webinars and interactive tutorial models is becoming popular, but to be most effective, these newer forms of education need to be more professionally done. Participation in development of diagnostic atlases and documents such as those provided by the INHAND effort are another means to gain expertise in diagnostic toxicologic pathology.

As already indicated, for the bench-level, “slide-reading” toxicologic pathologist who has not had recent exposure to new developments in related fields, cross-disciplinary exposure will primarily come from CE-type courses, including tutorials and Webinars. The trick here is to avoid having the courses taught by someone so immersed in molecular biology, toxicogenomics, or bioinformatics that the presentation is jargon laden and incomprehensible to anyone but another expert in molecular biology, toxicogenomics, or bioinformatics. One way around this common pitfall in providing training is to have the presentation given by an actual toxicologic pathologist who can create the presentation for his pathology colleagues and avoid heavy emphasis on a specialized lexicon. As with any training, this can be like an adult learning a foreign language and is best delivered in repeated short presentations with appropriate visual material, keeping in mind that pathologists are largely visual folks. There is no a priori reason why a simplified presentation of how mass spectroscopy or magnetic resonance works cannot be put together to provide a basic understanding and appreciation of the technology and how it can be used in interpreting toxicology studies. I am reminded of how helpful I found a soft-cover book titled Molecular Biology Made Simple and Fun coauthored by the late Lonnie D. Russell when it was published in 1997. Of course, much has been learned since 1997, and molecular biology is far more complex. Nevertheless, a “made simple and fun” approach might be just the ticket to provide some basic appreciation of toxicogenomics and things molecular for some of us more traditional toxicologic pathologists. In addition, the American Society for Investigative Pathology (http://www.asip.org/CME/JMD_2011.cfm) has offered a course on molecular mechanisms of human disease that provides a means for the human pathologist to become more familiar with newer molecular biology mechanisms. These courses, while not making a pathologist a molecular biologist, do go a long way in helping understand what the technology has to offer and perhaps more importantly help the pathologist communicate with molecular biologists who are providing the diagnostic technology.

How will all this cross-disciplinary exposure and training be accomplished? Who will do it? Who will pay for it? The major burden is financial. While there may be some truth in the notion that “if you build it, they will come,” someone has to pay to build it in the first place. For the most part, this is being accomplished by professional societies devoting a large proportion of society dues to this purpose. Grant support is a possibility, but in the current economic environment, that is challenging. Employers need to step up to the plate with financial support and by designing job descriptions for the toxicologic pathologist that include job elements mandating cross-disciplinary exposure with performance-based incentives for active participation. Finally, it should be a moral imperative that senior toxicologic pathologist practitioners provide the training opportunities and time at the double-headed microscope for those lower on the diagnostic learning curve as their part in giving back to the profession.

The practice and art of pathology based on diagnoses of hematoxylin and eosin–stained tissues has not changed much over the past several decades. In the meantime, other disciplines and approaches are continually evolving to help address contemporary biomedical concerns. Mine is not the first, nor will it be the last, attempt to redefine a role for pathologists in an ever-changing multidisciplinary milieu (see Becich 2000; Boorman et al. 2002; Ettlin and Leininger 2002; Morgan et al. 2004; Ward 2010). Our challenge is to maintain our passion and expertise for the tangible contribution we bring to the multidisciplinary team. Our challenge is to take advantage of our unique background and experience and take a leadership role in bridging the divide between disciplines and synergizing the multidisciplinary contributions such that the whole is greater than the sum of the parts.

REFERENCES


For reprints and permissions queries, please visit SAGE’s Web site at http://www.sagepub.com/journalsPermissions.nav.