Impacts of New Concepts and Technologies on the Practice of Diagnostic Pathology

An Emory University Perspective

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The only constant in pathology is change. New diseases are discovered; new pathogens emerge; diagnostic criteria, expert opinions, and favorite systems of terminology remain forever in flux. Arcane concepts, techniques, and instruments that were once confined to the research laboratory continually find their way into our daily clinical practice. No sooner have we mastered clusters of differentiation, intracellular signaling cascades, driver mutations, and DNA repair pathways than we must pivot to confront cancer immunotherapy, next-generation sequencing, mass spectrometry in the microbiology laboratory, and torrents upon torrents of terabytes. Far more than other specialists, pathologists also have to stay attuned to the ever-changing methods, ideas, needs, and expectations of our many clinician partners, who turn to us for expert advice and rely on us always to stay abreast of their own diverse fields. Through it all, pathologists learn and adapt. The dynamism of our specialty is key to its mission, its challenges, and its joy.

This Special Section of the Archives celebrates change. Focusing on a handful of subspecialties in one large, university-based pathology department, we invited teams of faculty to highlight some of the major trends that are affecting their own current practices, and how they are adapting their clinical workflows to accommodate. In a profession as fluid as pathology, some waves of change that first come ashore in an academic, quaternary-care health center are destined before long to wash over pathology practices everywhere. So the authors have tried throughout to emphasize trends that already are, or seem likely soon to become, relevant to pathologists in a wide range of practice types and settings. The 10 resulting essays (5 making up Part I that begins after this introduction, and the remainder in Part II that continues in the April issue) provide snapshots of just how deeply various new methodologies and concepts have penetrated each subspecialty, in some cases with transformative effects.

Technology looms large. Not surprisingly, gene-sequencing methods are finding application across the full range of subspecialties represented here, with implications for diagnosis, treatment, and prognostication. For some, this is just the latest in a long string of innovations: In the opening essay of Part I, for example, Fasano and colleagues trace the history of how once-novel serologic assays and mixed-lymphocyte reactions in the histocompatibility laboratory have gradually given way to sequence- and informatics-based approaches to tissue typing, so that "virtual cross-matches" are now a routine first step in bone marrow and solid-organ transplant. Hematopathology is likewise famous as an early adopter of new analytic technologies, and for reinventing its diagnostic schemes accordingly, so it is no surprise to read in the review by S. Li and coauthors that cytogenetic, sequencing, and gene-array methods are now inextricably part of the workup of hematologic disorders, and are yielding revolutionary insights.

But who would have anticipated that neuropathology, too, would now rely so heavily on cytogenetic and mutational information, with genomic data poised to supersede histopathology in the workup, for example, of low-grade gliomas, as reported by Neill et al? Or that next-generation sequencing would be proving useful in the diagnostic evaluation of pancreatic cyst fluid and bile-duct brushings, as Reid et al report? Or that genotyping now offers a more efficient way to identify red cell donors for sickle cell or thalassemic patients who have been highly sensitized by multiple prior transfusions, as Fasano et al describe? For diagnosing salivary tumors, Griffith and colleagues see little impact thus far of gene arrays and targeted therapies, but they find that testing for distinctive chromosomal translocations (using fluorescence in situ hybridization) can be a powerful adjunct to immunostaining, particularly for small biopsy specimens, cytologic cell blocks, or smears. Breast pathology, too, is still dominated by concepts and terminology from traditional histopathology, but X. Li and colleagues (in the essay that opens Part II in this Special Section) make clear that newer genetically based classification schemes are waiting in the wings, jostling for validation, and may soon be ready to move to center stage. In documenting those developments, as well as newly recognized subtypes of renal carcinomas (Ellis et al) or

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hematologic disorders (S. Li et al) that are defined by pathognomonic mutations or chromosomal anomalies, these essays leave no doubt that new gene-focused technologies are already having a profound, pervasive impact on diagnostic pathology.

It's also hard to overlook the rise of theranostics, in which pathologists apply specific immunostains or genetic tests to interrogate the genomic stability or clonal diversity of an individual cancer or to predict the likelihood that it will respond to targeted therapies. Breast cancer pathology is already far along that road, as X. Li et al indicate, with gene-expression and mutational data now being evaluated for use in conjunction with hormone-receptor status to define new tumor categories and to select optimal treatments. Testing for actionable *BRAF* mutations is widely accepted as standard of care for melanomas, and tests for the microsatellite instability associated with Lynch syndrome have also recently become routine, particularly for our specialists in gastrointestinal (Xue et al) or gynecologic pathology (Hanley et al). As in the early days of hormone-receptor testing, methods may vary, but there is little question that pathologists today need access to an expanding menu of theranostic assays and must become expert at interpreting them.

Equally far-reaching are the effects of new techniques that surgeons, endoscopists, and interventional specialists are using to visualize and sample lesional tissue, particularly from sites that were almost inaccessible in the past. Ellis and colleagues, for example, cite a panoply of technical advances in urologic surgery, including robotic prostatectomy, blue-light cystoscopy for identifying urothelial lesions, needle-core biopsies of kidney masses guided by magnetic resonance imaging (MRI), and a novel positron-emitting tracer for prostatic cancer, each of which poses unique interpretive challenges and opportunities for pathologists. On the one hand, innovative methods such as these have helped uncover entire new constellations of disease processes lurking at those sites; on the other hand, they often confront pathologists with minute snippets of ill-characterized entities and little basis for interpreting them. Those conflicting trends are evident in the articles by Xue et al, on liver and gastrointestinal pathology, and by Reid et al, on the pancreatobiliary tree, which underscore how the pioneering uses of MRI- or ultrasound-guided biopsies and endomicroscopy have increased the need for close coordination between pathologists and endoscopists, while greatly expanding differential diagnoses, particularly for previously uncharacterized intraductal lesions and preinvasive/in situ malignancies. And Hanley and colleagues offer a chilling catalogue of the ways that minimally invasive uterine surgery can artifactually "upstage" tumors of the corpus, such as by mechanically extruding neoplastic cells into the surrounding vasculature. As always, our clinician friends find endlessly inventive ways to keep pathologists on their toes.

The digital revolution in surgical pathology has begun, but not yet in the form that's envisioned. Whole-slide scans are now commonplace and we use them to quantify some tissue biomarkers and occasionally for real-time consultation between hospitals. But long acquisition times, regulatory hurdles, and cumbersome, unfamiliar user interfaces have kept them out of our routine diagnostic workflows so far. As Farris et al describe, such scans show promise for assessing renal and liver fibrosis or hepatic fatty change, as well as for "big data" research aimed at correlating histologic features with radiographic and molecular parameters. For us, and for now, though, their greatest impact has come in storing, retrieving, and sharing histologic images for conferences and teaching.

The traditional skills are still vital, but they need constant updating, too. To that end, Xue and colleagues offer a brief compendium of histomorphologic changes that pathologists may observe in the livers of patients treated with some of the newest targeted anticancer drugs, monoclonal antibodies, or treatments for hepatitis C virus, which are all now in widespread use. S. Li et al remark on the importance of knowing if patients have undergone treatment with monoclonal antibodies, as these may temporarily mask expression of their target antigens on hematopoietic cells or may even select for long-term alterations in the immunophenotype of a malignant clone. Even gross examination nowadays requires staying abreast of changing clinical practice, so that one can recognize, for example, the sequelae of various embolization procedures that may be encountered in liver explants, as Xue et al describe.

The pathologist's work will always be a work in progress. Together with our faculty colleagues in Emory University's Department of Pathology and Laboratory Medicine, we feel honored to have been given the opportunity to contribute these articles. We thank the editors of the ARCHIVES for inviting us to compile this Special Section, and to capture these snapshots in time of a department, its doctors, and a discipline that continually strive to advance biomedical science and improve patient care. We hope our perspectives will be of interest to other pathologists.

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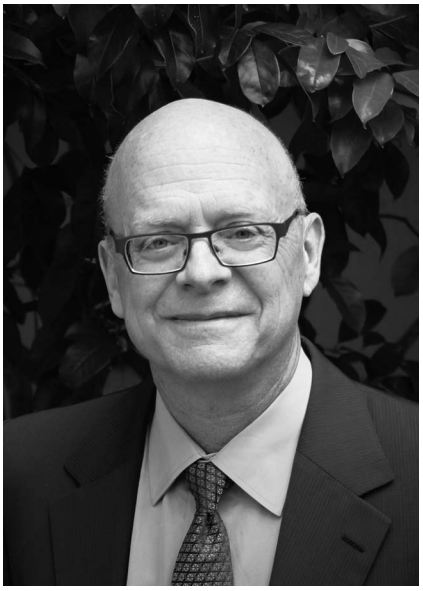

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