In 2001, at the turn of the century, the view of the future of surgical pathology was not an optimistic one. Dennis Heffner (1), in a very lucid account of surgical pathology’s past, present, and future, pointed out that surgical pathology has never achieved fully recognized status, and that this suboptimal recognition is likely to decrease further. Failure by surgical pathologists to acknowledge this tendency, Heffner warned, will essentially perpetuate it. In the same year, just a few months earlier, Juan Rosai (2) argued in favor of the continuing importance of morphology in daily diagnostic practice. These defensive and (to a certain extent) pessimistic articles were primarily prompted by the stated opinion of the director of the National Cancer Institute at the time (http://grants.nih.gov/grants/guide/rfa-files/rfa-ca-98-027.html), to the effect that morphological classification of tumors lacks accuracy in prediction of behavior, prognosis, and response to treatment, a viewpoint that was perceived by many as a nice way to thank surgical pathologists for the services rendered to date and open the door to a molecular taxonomy of neoplasias.

Six Years Down the Road, Where Are We?

For a start, molecular profiling of cancer is a reality in many situations. IgH and T cell receptor gene rearrangements, together with analysis of specific translocations, are increasingly applied to the diagnosis of lymphoma (3). Microsatellite instability, either for diagnosis of hereditary nonpolyposis colorectal cancer or for prognostication, is readily used in many centers (4). Fluorescence in situ hybridization is still the preferred mode of analysis of HER2-neu amplification status in breast cancer (5). EGFR mutation analysis is commonly used for therapeutic decision-making in lung cancer (6, 7), as is detection of KIT (c-kit) mutations in gastrointestinal stromal tumors (8). The presence of 1p/19q loss of heterozygosity has diagnostic and prognostic implications in brain neoplasms (9). Human papillomavirus subtype analysis by molecular testing has been advocated to play an important part in cervical screening (10). Translocation-related sarcomas can be more accurately diagnosed by PCR translocation detection (11). Molecular fingerprinting may revolutionize the way we approach analysis of putative metastases (12). This plethora of single-biomarker analyses (we have not mentioned all of them, but perhaps those most commonly used) will expand significantly in the near future. Also expanding are whole-genome approaches to molecular diagnosis, which are already a reality in the case of breast cancer (13) and are likely to be used soon in other neoplasias as well (14). Furthermore, all of these biomarkers are constantly redefined by the world of pharmacogenomics and the “personalized medicine” approach (15).

Thus, it is fair to say that since 2001 the transformation of medicine in general, and of surgical pathology in particular, has accelerated greatly. It may be useful at this point to introduce some earlier historical perspective. From the 1960s to perhaps the end of the 20th century, surgical pathology established itself as a central and fundamental discipline in clinical medicine. The specific weight of the anatomical-clinical dimension of pathology meant that no surgeon, oncologist, or clinician in general would decide on diagnosis, treatment, or prognosis of any of the cancers mentioned in the previous paragraph without a full conventional histopathological analysis (see Fig. 1A, featuring some of the cancers previously described). Regardless of what the future may bring, we believe that conventional morphological examination will be an extremely efficient method to diagnose, by itself, a large percentage of surgical pathology specimens, and thus will remain the backbone of clinical tissue analysis. However, from a phenotypic-clinical framework of diagnosis, we are shifting into a phenotypic-molecular-clinical dimension. Shown in Fig. 1B is the likely current model in many pathology practices in developed countries. As a result of this shift, the process leading from morphological surgical pathology to therapeutic decision-making includes an area of increasing molecular diagnostic complexity that, in most instances, is not directly addressed by surgical pathologists. The future consequence of this trend is clear: conventional surgical pathology will not be less important (the morphological characterization of the disease will always be a starting point of the diagnostic process), but molecular testing, rather than morphological characterization, may provide the decisive information for diagnosis and treatment. A lack of understanding and acknowledgment of this process will serve, in the words of Heffner (1), to decrease the status of surgical pathology.

It is true that the diseases mentioned above are select examples, and we are far from incorporating molecular testing in the routine diagnosis of diseases such as colitis or glomerulonephritis. Furthermore, many pathologists will argue that most sarcomas or lymphomas (two of the examples cited) can often be diagnosed comfortably without molecular testing. Nevertheless, we remain convinced that the molecular dimension of pathological diagnosis will be increased substantially in the coming years, once we know the full impact of pharmacogenomics and gene expression analyses in cancer (see Fig. 1C). Molecular testing will affect areas of diagnostic decision-making that are currently within the exclusive realm of morphologists.

In view of these considerations, we believe it is imperative that surgical pathologists incorporate active knowledge of
molecular tests into their diagnostic armamentarium. Maintaining professional relevance requires not only passive knowledge of these techniques (i.e., when or how to order them), but active molecular diagnostic skills for molecular assay validation and interpretation. Assimilation of this knowledge may accelerate the process of subspecialization that most of us are experiencing in different degrees. Following this line of reasoning, surgical pathologists would be responsible for those molecular tests applicable to their subspecialty (see Fig. 1D), a role that may require a reorganization of the way our departments function, as well as the manner in which we train future pathologists. As a result, however, surgical pathologists would cover the full spectrum of diagnostic analysis before treatment and, in doing so, regain the initiative in molecular diagnosis and the practice of diagnostic medicine.

Fig. 1. Representation of 6 disease examples in 4 different models of relation between surgical pathology and molecular diagnostics. Blue color signifies the realm of surgical pathologists in the different models proposed. (A), the traditional model of surgical pathology before molecular testing. (B), the current model in many pathology practices in developed countries. (C), the likely model in the near future following current trends. Finally, (D) proposes a fully integrated morphomolecular model for diagnostic pathologists.

Grant funding/support: M.S.-T. receives funding support from SCS Grants MN-05 and MN-77, awarded by the Singapore Cancer Syndicate, Agency for Science, Technology and Research, Singapore.

Financial disclosures: None declared.

Acknowledgments: I express my gratitude to Associate Professor Teh Ming for very useful suggestions on the manuscript.

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DOI: 10.1373/clinchem.2007.088088