Conclusion

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"In a time of drastic change, it is the learners who inherit the future.

The learned find themselves equipped to live in a world which no longer exists."

Eric Hoffer (1902–1983)

American philosopher

A dizzying array of technologies has been presented today, and our intention in this conclusion is not to repeat or even summarize what has been discussed, but to draw a few salient conclusions and lessons. We are witnessing an important and uncontested trend: Our clinical colleagues want increasingly detailed, reliable and relevant information from pathology specimen analyses that can be translated into optimal treatments. As pathologists we must re-educate and reinvent ourselves if we are to maintain the central role we now play as the ultimate arbiters of disease treatment.

The first "re-education" that must occur is the acknowledgment that a profound paradigm shift has occurred in our fundamental understanding of tumors. Our entire nomenclature of tumors, for example, is largely based on determination of cell type (classically referred to as the "cell of origin"). Taken to its logical conclusion, we have assumed that finer distinctions of cell type will provide better diagnostic information. This is the very reason why we perform mucin stains, why we do electron microscopy looking for microvilli, or why we characterize hormone expression in endocrine tumors: each of these represents an attempt to arrive at a more accurate assessment of the "cell of origin" of a histologically undifferentiated tumor. Such cell type analysis has succeeded insofar as it has served as a surrogate for predicting tumor biological behavior. Although it has done this remarkably well, the limitations of this approach are becoming obvious, and its power has run its course.

We have discovered, for example, that there exist tumors, *e.g.*, primitive neuroectodermal tumors/Ewings sarcoma, for which a normal cell counter-

part cannot be identified. Moreover, identification of differentiation products (*e.g.*, hormones) can tell us where a tumor cell is heading, but not necessarily where it came from. We now know that different molecular events can lead to morphologically similar tumors (*e.g.*, colonic carcinomas), and even tumors that might show similar "cell lineage" features. We have heard today that these different molecular events and their corresponding phenotypic alterations that we are discovering with increasing frequency are powerful predictors of clinical outcome. And recent developments in the treatment of breast cancer (which undoubtedly will be replicated in other tumors) have demonstrated that specific treatments (*e.g.*, Herceptin™) can be directed at subsets of cancers that are defined by alterations invisible to the pure morphologist.

The Lessons of Hormone Receptor Analysis

In the 1980s, it became routine practice for breast cancer tissue removed at surgery to be taken from the pathology lab *before histologic analysis was performed* and sent to a laboratory where the dextran-coated charcoal method of estrogen and progesterone receptor analysis was performed. Why and how did this happen? Because our breast oncology colleagues were at least as much, if not more, interested in knowing the hormone receptor status of a breast cancer as they were in knowing whether it represented a medullary or ductal variant. The treatment option available—tamoxifen, which binds directly to the estrogen receptor—demanded information that the pathologist did not provide.

Hormone receptor analysis came back to the anatomic pathology laboratory. This only happened (1) when it became detectable by a method that integrated morphology with phenotypic analysis, *i.e.*, immunohistochemistry, and (2) when we demonstrated that immunohistochemical analysis, in large part *because* it was integrated with tissue morphology, was a more accurate and reliable method of analysis.

The lesson of the hormone receptor story is that pathologists are in a unique position to determine

the optimal method of new marker assessment and integration. This example makes it very clear that technology unmoored from morphology can obfuscate as well as clarify. By converting from an “analog” to a “digital” signal, a great deal of information can be lost. There are other examples. Our ability to detect clonality in B lymphocytes is exceedingly sensitive, but now questions are being raised as to whether some of these rearrangements are occurring in benign lymphoid processes and are not indicative of lymphoid malignancy (1). Pathologists are clearly in the “catbird seat” with an ideal view of both the technologic and clinical limitations of a technique, as well as the cost factors that can determine the ultimate value of a new technology.

What Will Be the Role of the Molecular Analysis?

Some have suggested that within 10 years our microscopes will gather dust in the closet, as tumor biopsies will be shunted to a laboratory where mechanized analyses of tissue or gene microarrays will compare specimen profiles with those of hundreds or thousands of tumors with known outcome. This may be a dream or nightmare, depending on your perspective. It sounds suspiciously similar to predictions 10 years ago that tumors would be shunted to mechanized immunohistochemistry laboratories where detailed phenotypic analysis would pinpoint the tumor before the pathologist could put the glass slide on the microscope stage. We have learned the potential, as well as the limitations, of immunohistochemistry over the past few years. That technique now plays a major role when integrated with histologic analysis. As Dr. Jaffe has explained, we integrate phenotypic analysis of lymphomas along with the histologic assessment because the former *increases the accuracy* of the latter. By analogy, similar integration will be the likely fate of molecular advances, as we learn their potentials and their limitations.

What Will Be the Role of the Pathologist?

What is the role of the pathologist in these rapidly changing times? We propose that the pathologist is well placed to fulfill two roles that are highly integrated.

First, as physicians our assessment must remain central to the treatment decisions reached by clini-

cians. Pathologists became specialized along organ systems in the past decades because it was recognized that to be effective, we had to learn a great deal about the clinical correlates of the diseases we were identifying by morphology. This has come to fruition most evidently in the realm of breast pathology where pathologists play key roles in Interdisciplinary Breast Cancer Conferences that lead to the ultimate treatment decisions regarding breast cancer patients.

The second role that the pathologist must fill is that of the scientist, or, in the words of Dr. J.F.A. McManus, writing more than 30 years ago, the “Hospital Biologist” (2). This position will require us to play an active part in the evaluation, development, and performance of genotypic and phenotypic analyses of pathology specimens. Those of us in practice must re-educate ourselves, and we must redesign our Residency training programs to permit the next generation of pathologists to embrace this role.

The current controversy over HER-2/*neu* testing in breast cancer, as described today by Dr. Schnitt, serves as an excellent example of the “state-of-the-art.” Who is best equipped, and who is going to ultimately determine the most informative and cost-effective test format for detecting HER-2/*neu* alterations: the biotechnology companies, the oncologist, the HMO or hospital administrator, or the pathologist? If we are unable or unwilling to accept this challenge, there are others waiting in the wings to take our places. If we renounce this opportunity, we will be left with the job of carrying tissues from the operating room to the laboratory, parsing out fragments to various laboratories for molecular and other studies before placing a glass slide under the microscope. And we will have cheated ourselves out of the excitement and power that these new techniques bring to the diagnostic realm.

“We must change in order to survive.”

*Pearl Bailey (1918–1990)
American singer, actress*

REFERENCES

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