Introduction

Allen M. Gown, M.D.
PhenoPath Laboratories, Seattle, Washington

"*Nothing endures but change.*"
Heraclitus (Greek philosopher)

Why is this Long Course different from all other Long Courses? All previous Long Courses have been "organ"-based, reflecting the morphologic roots of our discipline. The year 2000 Long Course breaks with tradition and focuses on the dramatic changes occurring in Pathology as a consequence of the explosion of knowledge of molecular and cellular biology that have been accelerating in the past two decades. The dawn of the 21st century affords an excellent vantage point to survey the past and present, and to look toward the future. It is a truism that medicine has entered the molecular age. Not a week seems to go by without news about the cloning of some novel gene that confers susceptibility to a form of cancer, or the identification of some specific protein or mRNA species that can identify subsets of tumors, which will respond to specific therapies or predict unique outcomes. Yet amid the cacophony of this change, we, as Pathologists, steeped in our years of training and experience, quietly persevere in providing our clinical colleagues with tissue-based morphologic information, and training our Residents to do the same. We do this because, at the current time, it provides the patient's oncologist or endocrinologist, gynecologist or gastroenterologist with the most important information critical to the best care of the patient.

It is actually remarkable how little the anatomic pathology lab has changed in the past 100 years. Recently, an advertisement for a medical literature software company contained the banner headline, "Which of these do you still use?" Below this was a still-life photograph containing a manual typewriter, an abacus, a slide rule, and a microscope. But just as the tools of the photographer in the current "digital age" are changing from using images created by silver-based films to digital images stored on microchips, the *role* of the photographer has not changed; if anything, the *impact* of the photographer has increased owing to the greater power the new tools provided. So it is with the pathologist in the pathology lab in the new millennium: armed with new tools, we will enhance our ability to provide the information that is of greatest value to patients' physicians. One goal of this Long Course is to provide you with insights into some of the new tools that the pathologist can and will be using in this new molecular age of medicine.

But is the microscope really going the way of the abacus? There is an astounding amount of information contained in a paraffin section. But by examination of the H&E-stained section, we are tapping only a fraction of the information there. Some of our bewilderment at the information revealed by novel molecular and cell biological techniques is not unlike that of the narrator in the 1884 book titled *Flatland: A Romance of Many Dimensions* (1). In this classic work by Edwin A. Abbott, described as an "interdimensional experience," there is a dialog between the narrator, a resident of the two-dimensional Flatland, and some three-dimensional objects that he initially has a difficult time understanding. The narrator sees a sphere penetrating his home, but to him it is a dot, then an ever-enlarging circle, and then a smaller and smaller circle, then a dot again, and then nothing. As pathologists with light microscopes looking at H&E-stained tissue sections, we are like the Flatland observers. We see the "projection" of the molecular alterations that drive tumors into the realm of morphology. Much of it may appear difficult to interpret, but as we understand the intersections of these new approaches with our morphologic knowledge base, as Dr. Juan Rosai will emphasize, morphology will not be lost to molecular and other techniques, but will serve as a "gateway" to them, much as the two-dimensional world of the narrator of "Flatland" served as a gateway to the third (and higher) dimensional worlds.

As an example of "intersection" of molecular changes with morphology, consider the case of lobular carcinoma of the breast. These tumors almost always are associated with a truncation mutation of the cell adhesion molecule, E-cadherin (2). Loss of this protein (which can be easily demonstrated in the pathology laboratory by immunohistochemical

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techniques [3]) leads to loss of cell–cell adhesion, resulting in the very pattern of noncohesive "ball-like" cells, which are the hallmark of lobular carcinoma. Molecular changes thus are reflected in morphology. And the authors of this Long Course will underscore that what happens at the immunophenotypic or molecular level enhances our understanding of what happens at the morphologic level, drawing from examples in the realm of hematopathology, breast pathology, GI pathology, endocrine pathology, pediatric pathology, and solid tumor pathology.

We hope that this Long Course 2000, here at the dawn of the 21st century, will offer you a voyage into the new dimensions of organ-based diseases that have always been out there, but for which new tools are becoming available, permitting us to explore and understand them, and to incorporate them into our diagnostic approaches to human disease. We have brought together authors who are leaders in their fields, and whose articles will speak to the synergism of these novel techniques with our traditional morphologic analysis.

Rudolf Virchow, the Prussian pathologist who is the father of cellular pathology and one of the most influential physicians of the 19th century, showed remarkable vision 150 years ago, when he wrote:

"*Every anatomical change is a material one as well, but is every material change, therefore, also anatomical? Cannot it be molecular? Can a deep reaching molecular alteration of the inner composition of matter not take place with the preservation of its inner form and outer appearance.... One can have the greatest respect for morphological and histological studies...but must one proclaim them, therefore, the only ones to be pursued, the ones of exclusive significance?*" (4)

In the spirit of Rudolph Virchow, we welcome you to the year 2000 Long Course.

REFERENCES

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