Preface

It's Mass Spectrometry's Turn to Change Clinical Practice

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Editor

Norbert Elias in his essay, *Scientific Establishments*, used the metaphor of a spiral staircase to illustrate the advancement of human knowledge. Medical science follows this mode of advancement. Existing knowledge and technology are applied to unanswered questions, extending our pool of information and refining our understanding, but eventually, the capabilities of existing technology reach their limits, and while illuminating previously dark areas of the discipline, they also leave behind more unanswered questions requiring newer, more sophisticated technology to probe these territories. Thus, a new cycle begins.

The history of laboratory medicine provides an excellent demonstration of this spiral advancement process. "Sensory diagnostics" (taste, smell, and color) was superseded by simple chemical reactions followed by the measurement of enzyme activity and eventually immunoassays. Approximately two decades ago, we started applying molecular genetic methods on a wide scale that is now expanded into whole-genome and single-cell nucleic acid analyses, and we are examining the options to use gene editing tools for diagnosis. The most recent technical development in laboratory medicine is employing a relatively old analytical method, mass spectrometry (MS), in combination with other analytical methods, to make new inquiries about biochemical and pathologic processes in the human body. The new technology is drastically changing the practice of laboratory diagnostics. MS has started the new revolution in the literal and figurative sense of the word.

MS uses basic physical principles such as molecular mass, charge, and time to ascertain characteristics of molecules in human samples to derive diagnostic conclusions. The high analytical sensitivity of this method allows detection of previously unseen components, and its unparalleled resolution allows us to dissect seemingly uniform mixtures of molecules. These two characteristics of the technology permit simultaneous measurement of multiple analytes that may differ only by a single proton.

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Finally, MS can do all these "miracles" without requiring alteration, for instance, derivatization, of the molecule under examination. Because modification or prior amplification of very low concentration constituents is not needed, the chance for misidentification of detected chemicals or missing the presence of important substances is minimized.

MS can also be combined with other advanced analytical techniques, such as gas or liquid chromatography (LC), to enhance resolution and selectivity. This linked technology, in the form of gas chromatography MS, was among the earliest applications of mass spectrometers in the clinical toxicology laboratory. Atmospheric pressure ionization was needed to allow the use of the liquid chromatograph for separation of sample mixtures before MS analysis, forming the LC-MS. Because atmospheric pressure ionization produces soft ionization, multiple mass spectrometers in tandem (tandem MS or MS/MS) had to be used to break up the ions in the machine for analysis of the fragments, facilitating positive analyte identification. However, prior chromatographic separation of molecules is not essential, and several other sample introduction practices are now utilized, including direct infusion, gas phase sample introduction, paper spray, or various desorption methods that are combined with ionization, such as in matrix-assisted laser desorption ionization, to mention a few. The tandem MS is only one of the various mass spectrometers now in use by clinical laboratories. Ion traps can be included in the tandem MS, and physical properties of ions can be exploited for identification of molecules, as in accurate mass MS, represented by the time-of-flight (TOF) or orbitrap instruments. These techniques are complementary and may have specific uses in special circumstances. With proper selection of the analytical techniques, it is now possible to measure analytes of several thousands of Daltons mass range at picomole (10^{-12}) to femtomole (10^{-15}) concentrations.

Many articles in this issue of the *Clinics in Laboratory Medicine* describe current uses of mass spectrometers in the clinical laboratory. The selection of these examples is arbitrary but with the goal to show a cross-section of clinical applications and necessities. A comprehensive representation of all types of clinical applications is impossible within the scope of this publication. Small molecule testing is the most prevalent MS function in clinical MS, and several articles are included here on this topic. Other articles investigate the current state of proteomic analysis by LC-MSMS and discuss the use of TOF MS in the microbiology lab. The rapid development of mass spectrometric methods by independent laboratories without the help of certified analytical standards introduces new problems: the potential lack of agreement between results of different origins. Transferability of results obtained from different laboratories is imperative for continuity of patient care; therefore, MS result standardization must be undertaken, either by between-laboratory cooperation, by the development and application of international standards, or by test approval by regulatory agencies such as the Food and Drug Administration. Several reports in this issue explore the current status of assay standardization via one of these processes, while also pointing out necessary actions to expedite the standardization procedures to keep pace with the rapid spread of MS methods into clinical diagnosis.

The authors of the articles are accomplished researchers, and they are also directors of clinical MS laboratories. They have many years of experience developing and validating new diagnostic assays, and their practical experience is reflected in the articles, whether written on testing specific analytes, describing how to develop robust analytical methods, providing guidance toward accreditation of an MS laboratory, or setting goals for the training of MS laboratory personnel. In addition to MS laboratory operation specifics, the readers will find extensive references with the articles aiding medical and technical directors to start and maintain high-quality MS laboratories,

but policy-makers at regulatory agencies and industry representatives can also find valuable information in this issue of the *Clinics in Laboratory Medicine*. The articles also guide pathology residency and fellowship program directors and other educators on what to include in the necessary curriculum to properly train future specialists for clinical MS.

This issue of the *Clinics in Laboratory Medicine* will show how far the MS revolution advanced in a relatively short period of time and will also provide guidance on what needs to be accomplished to fully integrate MS into the clinical laboratory diagnostic process. Promising recent results of novel applications of MS are not covered because of publication limits and because many of these results are at the level of proof of concept experiments at this time. It is hoped that a future issue of the *Clinics in Laboratory Medicine* will present those findings as they gain acceptance into clinical practice after additional testing and evaluation.

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