# Spectacular Spectrometry

## The corporate-led evolution of MS produced an irreplaceable tool.

MARK S. LESNEY

Although first conceived in the late 1890s, mass spectrometry (MS) is a technology born and bred in the 20th century. Mass spectrometers are perhaps the most fundamental tools for understanding the nature of chemical composition and have become the mainstay of a healthy instruments industry. In the 21th century, MS has the brightest possible future as it adapts to a biological world.

At its heart, a mass spectrometer separates ions—created from molecules subjected to one of a variety of stresses, from simple collisions to laser blasts—according to their mass-to-charge ratio ($m/z$) by passing them through a magnetic and an electrical field simultaneously. The ions are evaluated with a detector when they collide. Evolution in the technology involved modifications to each of these components.

At first, MS seemed an obscure technology at best. The first mass spectrometer (then called a parabola spectrograph) was constructed by British physicist J. J. Thomson, the discoverer of the electron, in 1912. But there was little significant development of the technique until World War II.

### Wages of War

In the early 1940s, physicist E. O. Lawrence at the University of California, Berkeley, took an MS-based separation approach to enrich fissile uranium, uranium-235, from the natural isotopic distribution of uranium. This method used a gigantic magnetic device called a Calutron (for California and cyclotron) to separate ions according to their $m/z$; once separated, the ions were collected. This preparative mass spectrometer was able to purify the uranium-235 used to construct the atomic bomb.

During the war, in 1940, the prototype of the first commercially successful mass spectrometer was developed. It ultimately became known as the Consolidated Engineering Corp. (CEC) Model 21-101, first sold in 1943 to the Atlantic Refining Corp. in Philadelphia. (Although Westinghouse Electric sold a portable mass spectrometer designed by John Hipple, in 1941, it was not a market success.) By 1944, a CEC 21-101 users group formed in Pasadena, CA; the group later became the American Society for Mass Spectrometry. Ancillary standards and tools were seen as an immediate necessity, and the U.S. National Bureau of Standards produced the first 15 official hydrocarbon calibration standards for mass spectrometers.

The obvious need for computational tools for MS led to the introduction by CEC of the Model 30-103, an analog computer that could be used to analyze mixed hydrocarbon spectra.

### The Expanding Industry

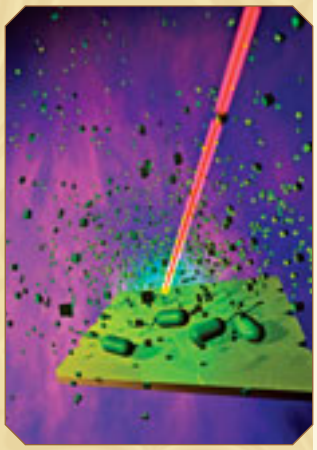
Immediately after the war, significant breakthroughs occurred in MS. In 1946, William E. Stephens of the University of Pennsylvania developed the first time-of-flight (TOF) mass analyzer. The principle of TOF relies on accelerating ions toward a detector with equivalent energy. In such a case, the "time of flight" becomes a comparative function of mass, that is, smaller ions move faster than larger ones. In addition, Metropolitan Vickers introduced the MS 1 mass spectrometer in the same year.

In 1947, CEC introduced the Consolidated-Nier isotope ratio mass spectrometer, and the Bureau of Standards and the American Petroleum Institute collaborated on a library of reference mass spectra. In addition, MAT (Mess und Analysen-Technik) was founded in Bremen, Germany. In 1948, the Omegatron, the first ion cyclotron mass spectrometer, was developed, and a dual inlet with a changeover valve was designed for rapid sample switching in high-precision isotope ratio MS by researchers at the University of Minnesota. The year 1949 saw the birth of ion cyclotron resonance.

In 1950, CEC introduced the Model 21-103 mass spectrometer, which would rapidly be coupled

**Top:** Finnigan quadrupole MS unit, *Chromatography*, 2001

**Center:** TOF MS, Bendix ad, *Analytical Chemistry*, 1969



**Above:** Artist's rendering of MALDI, *Modern Drug Discovery*, 2003

## TIMELY TANAKA

The 2002 Nobel Prize in Chemistry was given to three pioneers of methods for identification and structure analyses of biological macromolecules. Among them was Koichi Tanaka (Shimadzu Corp.), who was awarded the prize for his development of MALDI—in part through a fortuitous mistake in his laboratory. While attempting to develop an optimal matrix to contain a sample to be ionized by a laser blast, Tanaka mistakenly mixed glycerin instead of acetone with cobalt. According to the Shimadzu website, "Tanaka—part of a team noted for its faith in trial and error—came to the conclusion that even this presumably wasteful mixture, like any other, might have some potential—and might even be the 'right one'—and he set it on a sample plate and the road to becoming a miracle matrix."

One of Tanaka's two co-winners was John B. Fenn, who was awarded the prize for his development of ESI. Together with MALDI, ESI has helped to make MS not only a viable but an ideal tool for biological analysis.

to heated inlet systems capable of allowing gas-liquid samples to be introduced easily. In 1953, Wolfgang Paul published the first papers on quadrupole MS and ion-trap detectors. Quadrupole filters used a quadrupolar field to manipulate single ions or ranges of ions based on their $m/z$, thus acting as true mass filters.

In 1956, Roland Gohlke and Fred McLafferty first demonstrated GC/MS using a TOF mass spectrometer (Model 12-101) developed by the Bendix Aviation Corp. Also in 1956, MS was first used to identify an organic compound by bombarding the compound's vapor, at a pressure of $10^{-5}$–$10^{-6}$ mmHg, with electrons having energies of 50–100 eV. This process broke down the molecules of the compound to form reproducible positive, negative, and neutral fragments, making it possible to identify organic impurities in a sample without any preconcentration of the impurity.

Perhaps the key business trend of the 1960s was that of increased competition as MS gained popularity and expanded its forms and as more and more companies began manufacturing and distributing the instruments.

In 1962, the first commercial quadrupole mass spectrometer was sold to NASA by Electronics Associates, Inc. (EAI). In a clever circumvention of a ban on instrument exhibits at the 1963 annual meeting of the American Society for Testing and Materials, Applied Physics Corp. exhibited its MAT CH4 MS unit to attendees who were willing to walk to a bar across the street from the conference.

In 1964, Jeol produced its first mass spectrometer; and throughout the 1960s, PerkinElmer became a significant force in the MS market in the United States, acting as the distributor of Hitachi units. Competition continued to expand as, in 1967, the Finnigan Co. (acquired by Thermo in 1990) was formed by Robert Finnigan (formerly of EAI) to take advantage of the potential he saw in quadrupole GC/MS and the advancements computers would provide to MS instruments. That company's introduction of the first commercial quadrupole GC/MS came just one year later. Also in 1967, MAT, which came out with the CH5 that same year, was acquired by Varian, becoming Varian MAT. Significant to the biological future of MS, in 1968, electrospray ionization (ESI) at atmospheric pressure was developed by Malcolm Dole and colleagues, although the technique would not be routinely used for two more decades.

In 1967, PerkinElmer introduced its own mass spectrometer, Model 270—the first magnetic double-focusing GC/MS. By the late 1960s, Hewlett-Packard had entered the GC/MS market—and would continue its involvement through the 1990s. These instruments were a strong reflection of how the marriage of GC and MS would continue as the most powerful combination for organic analysis.

Also in the 1960s, the first secondary-ion MS, or SIMS, instrument was constructed under a NASA contract to analyze moon rocks. In SIMS, a sample surface is bombarded with a primary ion beam, followed by MS of the emitted secondary ions. The instrument was copied and marketed, creating an expanding demand for SIMS in the decades to follow, especially in the developing electronic materials industry.

### That '70s Flow

By the early 1970s, GC/MS was the technique of choice for monitoring illegal drug trafficking and use. With the development of the environmental movement prompted by Earth Day and the establishment of the Environmental Protection Agency (EPA), the issue of pollution monitoring became critical. An early example of this was the use of DuPont's DIMASPEC (digitized GC/MS) in 1971 to detect contaminant diethylstilbestrol in beef. In 1978, EPA accepted Finnigan's GC/MS system as a standard means of analyzing pollutants. Because of this endorsement, the company came to dominate the global market, even though units were priced in the $150,000 range. Such sales indicate the impact of the environmental movement in the 1970s—an impact that continues today—on the overall market for analytical instruments.

Throughout the decade, MS continued to develop new incarnations. In 1974, Fourier transform ion cyclotron resonance was introduced. By 1977, Finnigan was offering an early line of LC/MS systems.

New companies were formed to take advantage of new technologies. For example, Comstock was founded in Oak Ridge, TN, in 1979 by physicists Robert N. Compton and John A. D. Stockdale. Although their initial product was an electrostatic energy analyzer, they became noted for their TOF MS line introduced in 1987, and they would continue to develop specialized TOF instruments thereafter.

### The '80s and '90s

This decade saw the development of one of the most powerful inorganic analysis techniques. PerkinElmer became involved in inductively coupled plasma (ICP)-MS when through a joint venture with SCIEX, the company helped to develop and market the ELAN 250, the first ICP-MS instrument for commercial applications.

In 1987, PerkinElmer SCIEX introduced the ELAN 500, the first ICP-MS system with platinum cones and an inert sample introduction system. The company went on to launch the ELAN 5000, the first turbomolecular-pumped ICP-MS instrument, in 1990, and later the ELAN 6000, the first ICP-MS system with a simultaneous automatic extended dynamic range detection system.

New companies were unveiled and changes took place in corporate structure through mergers and acquisitions. In 1980, the Bruker Daltonics Corp. formed as part of the global Bruker organization. The company's roots were in the German Bruker-Franzen Analytik GmbH and the Swiss Spectrospin AG. These companies developed mobile detectors and mass spectrometers for physical chemistry. In 1981, Varian MAT was acquired by Finnigan, becoming Finnigan MAT.

In 1982, Cambridge Mass Spectrometry (CMS) was spun off from Cambridge Consultants Ltd. (CCL, a division of Arthur D. Little). In 1987, CMS became a wholly owned subsidiary of Kratos Analytical, which came under the control of Shimadzu Corp. of Japan in 1990. CMS produced surface analysis instruments using quadrupole and TOF-SIMS technology. In 1992, the company Kore was founded by a "core" of engineers and accountants at CMS who decided not to transfer to Manchester, U.K., as part of a cost-cutting effort to merge the CMS products with Kratos.

## MALDI and More

Because MS techniques were typically too harsh for most biomolecules, it wasn't until the development and routine deployment of the so-called soft ionization techniques—ESI (which was only then achieving popularity) and matrix-assisted laser desorption/ionization (MALDI)—that MS became a key tool in modern biology. MALDI was developed in 1985 (see sidebar). In 1988, the LAMS-50K, the first commercial MALDI-TOF MS instrument, was released by Shimadzu. MALDI rapidly became an important biological analysis technique, such that by 1990, protein structure studies were being performed using MALDI techniques.

Founded in 1987 in Branford, CT, Analytica began as a spin-off from Yale University to commercialize ESI MS. But it wasn't until 1989 that ESI was first reported to be useful for studying large biomolecules in a significant article published in *Science* (vol. 246, pp 64–71) by John B. Fenn and colleagues (see sidebar).

New MS companies continued to proliferate. Bergmann Messgeraete Entwicklung KG was founded in 1991 by Thorald Bergmann to develop and produce advanced TOF mass spectrometers based on an instrument he designed as his Ph.D thesis.

## Burgeoning Bio

If anything were to define MS in the 1990s, perhaps most notable would be the explosive growth of biological applications. For example, in 1992, low-level peptide analysis became possible, and by 1993, driven in part by the demands of the burgeoning Human Genome Project, limited oligonucleotide sequencing became possible. By 1996, MS of viruses was being attempted. All of this was becoming possible as MS became ever more linked to liquid chromatography—HPLC.

For example, in 1996, Waters made its largest acquisition up to that point by acquiring Micromass of Manchester, U.K. The acquisition achieved its goal, immediately putting Waters in the forefront of the market for LC/MS instruments.

With similar intent, in 2001, Varian expanded its MS technology by acquiring Bear Instruments of Santa Clara, CA, in order to increase its participation in the growing life science applications market. Bear produced analytical instruments based on triple-quadrupole MS/MS technology, including triple-quadrupole GC/MS/MS and LC/MS/MS systems. Quadrupole LC/MS/MS is a critical technology to the pharmaceutical industry for assessing ADME (absorption, distribution, metabolism, and excretion) parameters for drug development. Similarly, in late 2002, Waters and Micromass merged completely, with the stated intention of responding more readily to the increasing demand for LC/MS.

## Future of MS

Overall, MS is still an evolving technology. Its limits are being pushed and adapted to the latest demands of biotechnology with innovations such as tandem expansions and multiple connections to HPLC. With newer portable systems, such as the Inficon (formerly Leybold Inficon) Hapsite, being devised, the classic GC/MS instrument also remains strong—adapting to the world of bioterrorism. It seems likely that MS will remain for all time the stand-alone staple of modern chemical analysis, as well as the ultimate chromatography detector—expanding the practical and theoretical range of chemistry as a whole to the benefit of an unlimited set of applications, now and in the future. ◆

**Above:** GC/MS, Finnigan ad, *Analytical Chemistry*, 1971