Waters Corporation

Fifty Years of Innovation in Analysis and Purification

By Patrick D. McDonald

In 1958 James Logan Waters began the right business at the right time. Fifty years later Waters Corporation celebrates its golden jubilee of innovation in the field of analytical chemistry. Landmark liquid chromatography products from the company James Waters founded have transformed the practice of chemistry in the 20th century and continue to lead the way toward solving the significant separation problems of tomorrow. Pat McDonald, a senior fellow in Chemistry Operations at Waters Corporation, offers this look back at the man and the enterprises behind fundamental developments that continue to shape the practice of liquid chromatography today.

A publicity photo for Waters Associates organic synthesis marketing program taken in Robert Burns Woodward's chromatography lab, 1973. Pictured are (from left to right) Helmut Hamburger, Josef F. K. Huber, James Waters, and Woodward, in front of the ALC-100 Analytical Liquid Chromatograph at right. Hamburger was a postdoctoral fellow from the University of Switzerland. Huber, from the University of Amsterdam, built the first benchtop HPLC component system, in 1964, and was hired by Woodward's B_{12}-synthesis rival, Albert Eschenmoser.

The first "headquarters" of Waters Associates, located in a space Waters rented in the former Framingham, Massachusetts, police station.

BOTH IMAGES: WATERS CORPORATION

James Logan Waters grew up a headstrong and independent child in Lincoln, Nebraska, during the Great Depression. "Once the drought came, everyone suffered," recalled Waters in an oral history conducted in 2002 by the Chemical Heritage Foundation. Watching how well his parents dealt with those hard times must have forged in their future entrepreneur the strong moral fiber, work ethic, determination, and pleasant nature that have marked his life's work.

Young Waters's grades and attitude toward schoolwork steadily improved as he began to realize he had to achieve something meaningful to "feel good about himself." Excited by a junior high school project that observed local city businesses, Waters remembers, "I'd already decided that I wanted to be in business for myself, but I didn't know what business to choose. I think there was within me some great desire to do almost a little bit of everything."

While a high school junior, Waters moved with his family to Framingham, Massachusetts, where his father became treasurer of the B&W Bus Line. By the time he graduated in 1943, Waters had saved $1,000 in earnings from two paper routes, one before dawn and one after school. He pursued his interest in science and math at the nearby Massachusetts Institute of Technology (MIT). Soon after admission he entered the initial V-12 Navy College Training Program. Following his second MIT term, he transferred to Columbia University, where three years later, through an accelerated course of study, he earned a degree in both physics and engineering and a commission as a U.S. Navy ensign.

Two terms of humanities study at the University of Nebraska and an unsatisfying stint as an algebra teacher in Lincoln bookended Waters's final navy tour of duty in the Pacific and his honorable discharge in California in early 1947. An all-day aptitude test for veterans correlated him best with two career groups: professors and ministers. Although Waters confessed, "I am a bit of a preacher," he was unsure of what to do next and returned to Framingham to look for a job.

Robert Leveille, James Waters, and Wilbur Austin with the flame photometer they built for Consolidated Edison's Indian River Plant, ca. 1959.

James Waters and His Earliest Enterprises

In 1948 one of Waters's professors at MIT referred him to a contact at Baird Associates, an instrument manufacturer. Despite having no background in instrumentation, Waters was hired as an assistant to the project manager for Baird's double-beam infrared spectrophotometer, the first of its kind, based on an exclusive license to the design by Norman Wright at the Dow Chemical Company. For organic chemists this instrumental technique proved more powerful than ultraviolet-visible spectroscopy for functional group identification and chemical structure elucidation; it drove the dramatic shift from traditional wet methods to modern instrumental analysis in the systematic identification of organic compounds.

Much to Waters's disappointment, the management at Baird was not interested in refining the spectrophotometer's design; it was viewed as a finished product, and the time had come to sell it. Although Baird had the only double-beam spectrophotometer for over two years, the company was nearly put out of business by Perkin Elmer, whose R&D in the meantime resulted in a more compact unit that sold far better. The lesson was not lost on Waters.

In his months working at Baird as a self-described "glorified service man and assembler," Waters read reports by teams sent into Germany by the U.S. government to uncover the technologies that had been developed by the Axis powers during the war. One account, of Karl Luft's development of an infrared gas analyzer, captured his imagination. At the time Baird was also making an infrared gas analyzer, but Waters thought Luft's invention was a more selective detector. Waters decided: "This is my opportunity—all I have to do is reduce the Luft technology to American practice and I'm in business." He soon found that goal was easier said than met.

He decided to leave Baird and start his own company, J. L. Waters, with the $5,000 he had saved and an additional $14,000 lent to him by family members. He set up shop in the basement of his parent's house in Framingham, but when he hired his first employee his mother forced him to find new quarters for the business, and he leased an empty room in a local hardware store.

Finally Waters succeeded in his design, and he sold his first infrared analyzer to DuPont. The second unit was purchased by the Naval Research Laboratory for the detection of toxic gases such as carbon monoxide on submarines. He attracted a major ally, Mine Safety Appliances (MSA), by word of mouth in 1949. Wanting to enter the gas analyzer business but having problems in R&D, MSA formed an alliance with Waters's fledgling company: J. L. Waters, Inc., continued to do the research and manufacturing while MSA sold the products. In 1955 Waters made a shrewd deal to sell his still unprofitable company to MSA for $200,000, 15 years of royalties at 3%, and a three-year contract as a consultant. He used this time to plan his next enterprise, one that would quickly become profitable and live on under his name for many years to come.

The Humble Start of Waters Associates

Waters took his earnings from the sale of J. L. Waters and, in September 1958, established Waters Associates without a product to sell. He rehired five of his former employees—mostly technicians without college degrees—and operated out of a rented space in a former police station. Some early projects included a balloon hydrometer for the U.S. Air Force; a flame photometer for Consolidated Edison; and a conoblender for the Coca-Cola Company. (Specifically, the latter instrument's purpose was to blend the high-sugar-content, highly viscous Coca-Cola syrup with water while measuring the mixture's refractive index (RI) to assure uniformity.) Although the process-control instrumentation market wasn't particularly lucrative, Waters gained valuable experience that made his breakthrough into chromatography possible. At first Waters had licensed his sensitive RI process monitor to MSA, but he wisely acquired it back later. He also lured Larry Maley from MSA to become the first Waters sales manager. Together they embarked in earnest on the refractometer business.

In 1962 John Moore, a polymer chemist at Dow Chemical in Freeport, Texas, was told about the novel design of the Waters refractometer by his engineering colleagues and called the company to request a custom unit with unusual specifications. He wanted a flow cell with one-tenth the standard volume that could operate at 130°C—purportedly for use with orthodichlorobenzene. Waters knew that orthodichlorobenzene was a liquid at room temperature and argued that a smaller volume was not necessary for process control, but Dow's money talked, and Waters made the modification.

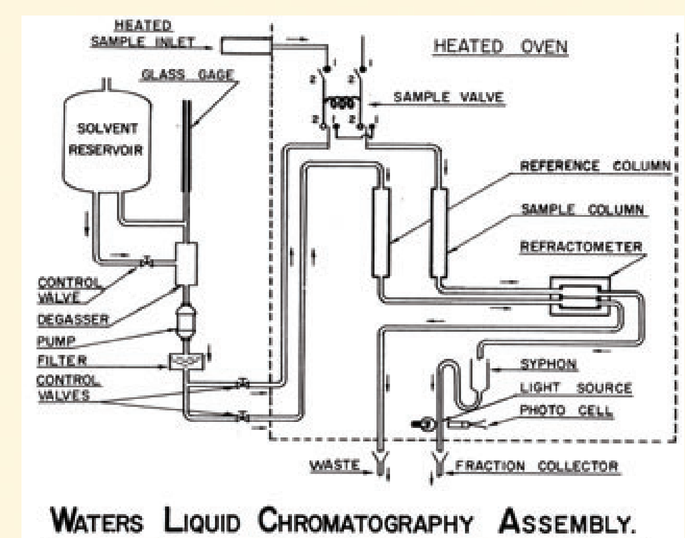
Several months later curiosity consumed Waters, and he sent Maley to Freeport to learn what Moore was doing with his modified refractometer. With patent applications filed just days earlier, Moore was free to describe his homemade instrument and new technique: he had synthesized controlled-porosity cross-linked polystyrene-divinylbenzene beads and packed them into columns. When a dissolved polymer sample was injected into the column, the larger molecules could not penetrate the pores and thus moved more quickly; the smaller molecules entered the pores and therefore took longer to emerge. The resulting chromatogram represented a molecular size distribution of the sample components that could be correlated with their molecular weights. Moore called his process gel permeation chromatography (GPC). His work with synthetic polymers in organic solvents had been inspired by the classic work in Sweden by Jerker Porath and Per Flodin on aqueous gel filtration separations of biopolymers.

Maley immediately proposed that Waters Associates manufacture the system that Moore had conceived. Moore convinced upper management in Midland, Michigan, who favored a much larger firm, to contract with this tiny instrument company, and in January 1963 Waters made a $10,000 down payment on royalties for his exclusive license to the GPC technology. Waters himself went to Moore's lab for three weeks of fact finding; he learned every aspect of the process, including how to synthesize the polymer beads (later to be sold by Waters Associates under the trademark Styragel), and returned to Framingham filled with ideas on how to construct an improved version of the instrument. Within three months, Waters and his team had built and sold five prototypes of the GPC-100—in essence the first commercial high-pressure liquid chromatography (HPLC) system (see "CHF's Most Wanted," page 16).

It used to take up to three weeks to get a molecular weight distribution for a single polymer; GPC could achieve the same result in about 90 minutes. Polymer chemists soon saw the potential of this new technology. Maley in turn took note of the issues that GPC users experienced and inaugurated an annual GPC symposium at which successful early adopters and struggling users could learn from each other, thereby fostering best practices, while Waters's team gleaned R&D ideas from both. (These meetings inspired many similar user forums that continue to this day.) The financial success of the GPC business enabled Waters Associates to move to larger facilities in 1965 and to expand its product line of instruments and column packings over the next decade to all modes of analytical and preparative liquid chromatography.

WATERS CORPORATION

JACK CAZES



Flow schematic from page 4 of the 1963 instruction manual for the first prototype of the GPC-100. As apparent in the diagram's title, all the elements of an HPLC system were present in this instrument.

The B_{12} Story

The next big break for Waters Associates followed in fall 1970 from a user query: Helmut Hamberger, a postdoctoral fellow in the Harvard University lab of Nobel laureate Robert Burns Woodward, called Waters in frustration to ask for help in separating isomers of key intermediates in the total synthesis of vitamin B_{12}. Waters had no idea who Woodward was, but when his vice president of marketing, James Little, told him about Woodward's exalted reputation among organic synthetic chemists, Waters concluded he should tackle the problem himself. This market was one he had wanted to penetrate ever since being told in 1968 by a prophetic researcher at Mobil that every organic chemist ought to have a liquid chromatography (LC) system on his or her bench. So he packed some columns, trundled an ALC-100 (a versatile system with both ultraviolet and RI detectors) to Woodward's lab, and proceeded to solve separation problems.

I was present at the symposium on natural product synthesis held in 1971 at the 23rd Congress of the International Union of Pure and Applied Chemistry in Boston. Before such luminaries as Derek Barton, Alan Battersby, Karl Folkers, and Gilbert Stork, Woodward, in a nearly four-hour lecture, recounted the B_{12} story, punctuating it frequently by declaring, "We could not have done this without liquid chromatography." Nearly every organic chemist of note was in the audience of close to 5,000, and although Woodward cited neither company nor brand names in his talk, the cognoscenti spread the word like wildfire. Following Woodward's example, a single HPLC peak soon supplanted a single thin-layer chromatography spot as a criterion for chemical purity in organic synthesis.

To take advantage of such excellent publicity James Waters himself quickly assembled a bold direct mail campaign. He compiled a list of 900 names and addresses from an American Chemical Society directory of chemistry faculty and mailed each a promotional kit that included a glossy photo of himself with Hamburger and Woodward and a letter with the simple message, "Look what we did for Woodward. We can do the same for you!" Following up on the 100 replies to his first foray into marketing catalyzed phenomenal growth for Waters Associates.

The Next Generation of Innovation

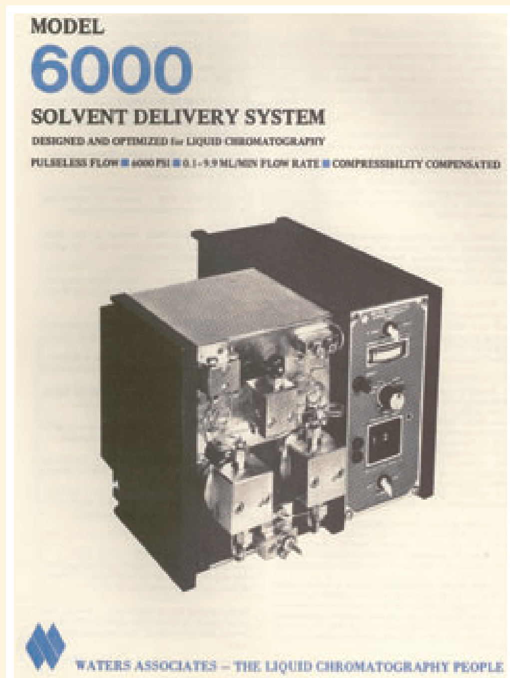
Although his company's reputation was built on dedication to making customers successful, Waters and his team recognized that their LC systems used many components made by other companies. They foresaw the importance of becoming self-reliant if they were to deliver state-of-the-art technology and continue as a market leader. Over time, each component of an LC system—pump, injector, detector, column, fittings, stationary and mobile phases—was rethought and redesigned. A commitment to materials science began when Styragel polymer technology was used to create

Porapak packings for gas chromatography columns, and a 1969 collaboration with István Halász in Saarbrücken led to the development of Durapak— the first commercial bonded-silica phases for gas chromatography and liquid chromatography— and a new standard for efficiency: Corasil, the first pellicular silica HPLC packings.

Waters Associates introduced the first dual-reciprocating piston, 6000-psi pump for HPLC, the M6000, in 1972, developed by R&D director and engineer Burleigh Hutchins and a craftsman and machinist named Louis Abrahams. This precision-volume solvent-delivery device used noncircular gears, a step motor, and feedback control circuitry to drive small-diameter parallel plungers sequentially for nearly pulseless flow. When the M6000 hit the market it was considered revolutionary; it proved so reliable that many continued to be used for decades. The M6000 was to be the last R&D project that Waters would oversee, and it inspired a succession of innovations destined to alter the HPLC landscape forever. Competitors soon retired pressurized vessels and other primitive pumping means and sought to imitate the wildly successful M6000. Cottage industries sprang up to supply replacement parts. All this activity spurred rapid acceptance of HPLC in labs worldwide and accelerated the growth of the nascent HPLC industry.

The first 6000-psi compatible septumless high-pressure injector for HPLC, the Model U6K, with its novel valve and fluid circuit technology, soon followed. The U6K and the M6000 had been developed in parallel with another landmark chemistry project, led by Richard Vivilecchia, to create the first commercial small-particle (10-µm) packing materials for HPLC. These were µPorasil silica and the first monofunctionally bonded silica, µBondapak C_{18}, developed by using a unique, proprietary homemade silane. Columns packed with the latter, introduced in its present form in 1974, became the best-selling columns in history.

The first generation of HPLC users were frustrated by poor-quality solvents. In the late 1960s a Waters Associates applications chemist, William Dark, worked with Malinckrodt to stabilize chloroform with nonpolar amylenes rather than ethanol so as not to wreak havoc on retention-time reproducibility in normal-phase separations. This success led to the development of other HPLC-grade solvents. Waters Associates itself entered the solvent business for a few years in the late 1970s, during which time it developed specifications and analytical protocols that led to major improvements in the quality of methanol, acetonitrile, tetrahydrofuran, and other key mobile phase components, especially water. When Waters Associates exited the solvent business, it shared all its test procedures and demanding requirements with the industry, thereby creating a competitive environment from which users ultimately derived significant quality and performance benefits.



[LEFT] Thirty years of solid-phase extraction: Waters Sep-Pak silica cartridges and original foil pouches, January 1978. [RIGHT] Cover of first brochure for Waters Associates Model 6000 Solvent Delivery System. The M6000, U6K, µBondapak trio of innovations was responsible for changing the widely accepted meaning of the letter *P* in Csaba Horváth's original 1970 acronym "HPLC" from "pressure" to "performance."

In 1977, commissioned to find "new, faster, more convenient ways to do traditional sample preparation operations," I teamed with my colleagues, Waters Associates researchers Vivilecchia and David Lorenz, to invent the Sep-Pak cartridge by using triaxial bed compression and hermetically sealed individual packaging to maintain bed integrity, performance uniformity, and adsorbent activity. Three months later, in January 1978, Waters Associates shipped the first commercial, disposable, miniature silica-based adsorbent liquid chromatographic columns for sample enrichment and purification via solid-phase extraction (SPE). Almost three years passed before a competitive product came to market. Explosive growth followed in the application of SPE to a full spectrum of sample preparation problems in every lab around the globe. Thirty years later SPE is still growing rapidly and stands as a predominant technique for removing interfering substances in samples prior to analysis.

James Waters sold his company to Millipore in 1980, thereby ending his relationship with Waters Associates. Millipore, in turn, divested the Waters Division in 1994. Waters Corporation became a publicly traded company again in 1995. A year later new high-purity silica Symmetry HPLC columns, Alliance HPLC systems, and patented Oasis polymers raised the respective bars for column, flow rate, and SPE reproducibility to amazingly high levels. Also in 1996, Waters morphed from a minor player to a major leader in mass spectrometry by acquiring Micromass Ltd., of Manchester, England.

BOTH PAGES: WATERS CORPORATION

Several times in the past 50 years Waters has introduced equipment designed expressly to operate new column technology, creating a dramatic increase in separation power with the potential to alter the course of science. The most recent of these system innovations, introduced in 2004, has pushed the limits of separation science from high to ultra performance and was inspired by investigations into materials science. Zhiping Jiang and his team won awards for the first generation of hybrid-particle technology (HPT) packings, polymerizing a pair of monomers (tetraethoxysilane and triethoxymethylsilane) so that organic functionality may be distributed throughout a spherical silica particle's backbone. HPT offered, for the first time, the possibility of designing tailored particle surfaces, even deep within micropores. By incorporating an ethylene bridge into one of the comonomers, Kevin Wyndham and his team were able to make 1.7-µm particles with an order-of-magnitude-higher resistance to hydrolysis at pH extremes and surprisingly high pressure resistance. This latter discovery, in turn, inspired Waters Corporation engineers to design the Acquity UltraPerformance LC System, capable of operating at 15,000 psi. Its dramatic order-of-magnitude increases in speed, sensitivity, and resolution herald the dawn of a new era in separation science.

The Acquity UPLC system.

The principal inventors and developers of the Acquity UPLC system, holding the 2005 R&D 100 Award plaque. More than 40 new patents have been filed or issued to date on its novel technologies.

A Legacy of Innovation

Although published contributions from academia are often placed in the limelight, so many of the important achievements in chromatography have been made almost invisibly by industrial scientists and engineers. Crossing the boundaries of physics, chemistry, mathematics, and engineering, separation science has been perfectly mated to the interdisciplinary teamwork vital to entrepreneurial endeavors that are focused on uniting resources to solve problems and create products that meet customers' needs. James Waters exercised his inborn drive to succeed and, through his enterprises, brought these forces together to create revolutionary tools for analysis and purification.

As Waters Corporation approaches its golden jubilee, Waters and the company he started can take pride in the legacy of innovation and vision its first 50 years will leave. Although nearly 30 years have passed since James Waters sold his company, his name remains over the door, and the company continues to follow his simple formula for success: "innovation, a good attitude, and hard work". ☼

Patrick McDonald is a senior fellow in Chemistry Operations at Waters Corporation. This article has been adapted from his story "James Waters and His Liquid Chromatography People: A Personal Perspective" (search for WA62008 on www.waters.com) with supplemental material from private conversations between McDonald and Waters and other long-time colleagues and an oral history interview conducted with CHF in August 2002.