The importance of liquid chromatography (LC), and especially high-performance LC (HPLC), in today’s world hardly needs stating. It is the most widely used technique for the analysis of chemical mixtures and has contributed in a major way to science (especially the biological sciences) and everyday laboratory practice. LC is primarily a practical technique, so our story is limited to those innovations that contributed significantly to its present use in “working” laboratories. In reflecting on the history of LC, it appears to us that only a few “essential” actors exist in this drama: single individuals whose absence might have delayed the technique by more than a year or two. Thus, the development of the present-day LC has largely been an evolutionary, rather than a revolutionary, process. Furthermore, many important innovations within the past 50 years have occurred within industrial research and development (R&D) groups, where it is often not possible to assign credit to a single person for a final product. Finally, every attempt at history
suffers from incomplete and conflicting accounts of who did what—and when. In the present discussion, we try to emphasize “what” and “when” rather than “who.”

1.1 INTRODUCTION
Several important innovations in the history of LC have been reviewed by Ettre [1]:

- Invention of chromatography in the early 1900s [2].
- Invention of partition and paper chromatography in the early 1940s [3].
- Development of ion exchange chromatography (IEC) [4] and the amino-acid analyzer during the 1950s [5].
- Invention of gel filtration chromatography in the late 1950s [6,7].
- Development of the gel-permeation chromatography (GPC) in the early 1960s [8,9].
- Development of HPLC in the mid-1960s [8,10–17].

The present chapter emphasizes the work on HPLC, while noting major, prior contributions that made this technique possible. Most advances in HPLC can be organized as follows:

- Development or application of the basic theory combined with empirical observations of the separation process.
- Invention of new chromatographic modes (e.g., ion-pair chromatography, hydrophilic-interaction chromatography (HILIC)) and the development of HPLC columns for new applications (chiral separation, large biomolecules).
- Development and improvement of equipment and columns.

1.1.1 DEVELOPMENTS BEFORE 1960
A good account of the discovery of chromatography by Tswett is given in Refs. [2] and [3, pp. 4–6]. Despite a few subsequent applications of chromatography in other laboratories [3, pp. 7–9], this technique became generally accepted only after its reintroduction in 1931 by Kuhn et al. [4]. The invention of liquid partition chromatography was reported by Martin and Synge in 1941, followed soon after by its extension to paper chromatography in 1944 and the first application of two-dimensional chromatography [5].

Significant work on ion exchange separation began in the 1930s, with the subsequent development and application of IEC for separation of the rare earths and transuranium elements [6]. The extension of IEC to organic compounds was next, implemented by Cohn and Samuelson [3, pp. 17–21]. By 1958, Moore, Stein, and Spackman reported the automatic analysis of amino-acid samples by means of IEC [7]. Their system was a precursor of HPLC that incorporated automatic pumping, efficient IEC columns, and continuous colorimetric detection. This system was later improved and commercialized as the Beckman-Spinco model 120B amino-acid analyzer.

Yet another major development, in the later 1950s, was the invention of gel filtration [8,9] for the separation of large biomolecules by molecular size; this was
followed a few years later by the development of GPC for similar separation of synthetic polymers [10]. The latter then led to the development of a commercial GPC system by Waters Associates (the GPC-100 [11]), which would morph into an early commercial HPLC system (the ALC-100).

### 1.1.2 HPLC AT THE BEGINNING

Prior to the development of the first HPLC systems, gas chromatography (GC) provided an example of what HPLC might be capable of automation, speed, and detection sensitivity, as well as the separation of higher boiling and thermally unstable compounds. By the early 1960s, the automation of LC had been demonstrated for amino-acid analysis and GPC (Section 1.1.2). By then, it was appreciated that smaller particles in well-packed beds could increase both separation speed and efficiency. Quick separations with small-particle columns also require higher pressures to pump the mobile phase through the column. Detectors that could be used with LC for most samples presented a major challenge at this time—and for several years thereafter (Section 1.5).

Before 1965, the possibility of using HPLC for separating samples other than amino acids or polymers had undoubtedly occurred to many people. However, the exploitation of this idea required its reduction to practice, followed by the production of commercially available equipment, as in the case of the amino-acid analyzer and the GPC (Section 1.1.2). Viewed in these terms, HPLC was first reduced to practice in ~1964 in the United States under the direction of Csaba Horváth [12] and in The Netherlands by Josef Huber (see Ref. [13, pp. 159–166 and 209–217]). The system developed by Horváth was subsequently the basis for the LCS 1000 Nucleic Acid Analyzer sold by Picker Nuclear (later acquired by Varian), and contributed to the first general-purpose HPLC (Waters ALC-100) [11]. Jack Kirkland had visited Huber’s laboratory in 1964 and subsequently began an HPLC program at DuPont [14–17], which culminated in the Model 820 at about the same time as the ALC-100. By 1970, sales of HPLC systems were dominated by Waters Associates and Du Pont. Superficially, porous Zipax [17] was initially the most popular column packing. In our opinion, Horváth, Huber, and Kirkland can be considered the “fathers” of HPLC. Some closely related work at that time by others [18–24] is also relevant to the origin of HPLC. For a description of the columns, equipment, and practice at that time, see Ref. [25].

### 1.2 HPLC THEORY AND PRACTICE

Separation as a function of experimental conditions was understood in general terms for GC, and similar principles were expected to apply to HPLC. Resolution, $R_s$, can be described by the Purnell equation [26] in terms of the plate number, $N$, separation factor, $\alpha$, and the retention factor, $k$:

$$R_s = 0.25 \left( N^{0.5} \right) \left[ \left( \alpha - 1 \right) / \alpha \right] \left[ k / \left( k + 1 \right) \right]$$  \hspace{1cm} (1.1)
A semiquantitative understanding of column efficiency (plate number, \(N\)) existed prior to 1965, based on the further development of the van Deemter equation for GC [27] and its extension to LC by Giddings [18]. Later work resulted in the highly useful and widely applied Knox equation [28]:

\[
\frac{h}{h_0} = A\varepsilon^{-0.33} + B/v + Cv,
\]

where the reduced plate height, \(h\), is related to the reduced velocity, \(v\), of the mobile phase. The later development of “Poppe” (or “kinetic”) plots further advanced our understanding and use of column efficiency [29]. For further details on Eq. (1.2) and values of \(N\), see Chapter 2 and [30]. When developing an HPLC procedure, the main challenge has been the selection of separation conditions for the control of peak spacing, that is, “optimum” values of \(\alpha\) (Section 1.2.2).

Basic theory played an important role in the development of HPLC, but its implementation was primarily the result of (a) the introduction of new separation modes or techniques (Section 1.2.1), (b) a better understanding of how best to vary conditions for a satisfactory separation (Section 1.2.2), and (c) improved columns (Section 1.3) and hardware (Sections 1.4 and 1.5).

### 1.2.1 NEW HPLC MODES AND TECHNIQUES

Many of the separation “modes” used today in HPLC were described prior to 1960; for example, reversed-phase chromatography (RPC) was first used by Martin in 1950 [31]. Although a few names are often associated with the rapid development of RPC over the past four decades (e.g., Horváth, Kirkland, Knox), the present dominance of this technique can be attributed to the efforts of numerous practitioners in both industry and universities—as well as its inherent advantages.

A history of the development of gradient elution is provided in Refs. [32–34]; the group of Tiselius is generally given priority for its first implementation and theoretical treatment in the 1950s. A practical understanding of gradient elution has since been facilitated by the linear-solvent-strength model [34].

The technique of ion-pair chromatography became a useful supplement to RPC for the separation of ionizable compounds that were often poorly retained by RPC. Schill and Knox are usually associated with the introduction of this mode [35,36]. Another technique for the separation of more polar compounds, such as sugars (which have poor retention in RPC), was used in the 1970s and later improved by Alpert [37] to become HILIC.

Separations of large biomolecules by HPLC required the development of suitable columns, featuring rigid, large-pore particles, and less-hydrophobic stationary phases. Whereas RPC has been used for separating proteins, these large, hydrophilic compounds are more often separated by gel filtration or ion exchange. Beginning around 1975, Chang et al. [38], Kato et al. [39], and others pioneered the development of columns for bio-HPLC. The first such column (SynChropak GPC100) was sold in 1978. Chiral separation was another area that awaited the development of suitable enantiospecific columns (Pirkle, Davankov, Okamoto, Armstrong, and
others; see Ref. [30] for details). Nothing more will be discussed about the latter columns for chiral separation, and very little about columns for biochromatography.

### 1.2.2 SELECTION OF CONDITIONS FOR THE CONTROL OF SELECTIVITY

By the 1960s, it was appreciated that values of $\alpha$ for different pairs of solutes could be affected by the column, the mobile phase, and the temperature. There are many different columns, and the mobile phase may vary according to the concentrations of its constituent solvents, various buffers, and additives, as well as the pH. There are thus a very large number of possible combinations of these separation conditions; only gradually was it learned the conditions most useful for controlling $\alpha$ and the best way to minimize the number of necessary experiments for a successful separation. As the result of much practical experience and a few systematic studies (e.g., Refs. [40–43]), successful strategies for optimizing selectivity are now available for different samples (Chapters 14, 15, and Ref. [30]). Some noteworthy developments between 1970 and 2010 include

- The introduction of resolution maps (for $\alpha$ or $R_s$ as a function of temperature for IEC [44]).
- Development of computer-assisted mapping of $\alpha$ in RPC as a function of mobile phase mixtures of acetonitrile, methanol, and tetrahydrofuran [45].
- Development of computer-assisted mapping of $R_s$ in either isocratic or gradient RPC as a function of (a) simultaneous change in two or more conditions that affect $\alpha$ and (b) all conditions that affect $N$ (e.g., DryLab [30, Chapter 11]).
- Development of a reliable procedure for characterizing column selectivity [46] and its use in various practical applications [47].

### 1.3 COLUMNS

The development of HPLC depended on new columns, which in turn required new particles, new stationary phases (particle coatings), and improved procedures for packing the column. For details on column developments before 1994, see the review of Majors [48]. Table 1.1 summarizes several of these column innovations, with the dates of their introduction into the marketplace.

#### 1.3.1 PARTICLES AND COLUMN PACKING

In 1939, Martin noted that (a) small particles in well-packed beds would be needed for increased separation efficiency and (b) such columns would require higher pressures to operate. Prior to 1960, particles for chromatography usually had diameters $\geq 100\mu m$ and consisted of either polymeric spheres or irregular silica (prepared by sieving crushed silica). Polymeric materials typically gave lower plate numbers, so that inorganic oxides (mainly silica) became preferred for HPLC columns. HPLC
columns at first used coated glass beads (e.g., Pellosil) or beads coated with a porous layer of silica (e.g., Zipax). The thickness of the stationary phase was only a fraction of the particle diameter, thereby reducing the diffusion distance within the stationary phase and yielding higher values of $N$—but with decreased loadability.

Smaller, fully porous particles with a narrow size range were expected to provide more efficient columns (as well as superior loadability), but such particles could not be produced by sieving. The introduction of air classification for particle sizing overcame this difficulty, and around 1970, Merck offered irregular silica in diameters of 5 and 10 μm. Whereas larger particles were easily packed by tapping the column until the bed settled, packing particles of 10-μm diameter (or smaller) required a different approach. The first published procedure for reproducibly packing HPLC columns with particle diameters ≤10 μm used a balanced-density approach [49], similar to that used earlier for GPC columns; the resulting MicroPak columns were offered for sale by Varian in 1971. Over the years, many procedures have been described for packing particles with diameters ≤10 μm [30]; in practice, each new particle requires customized conditions for best results.

About the same time, spherical particles with 7-μm diameters were produced by DuPont and sold under the name Zorbax. The latter particles were prepared by the aggregation of colloidal particles, much as popcorn balls are assembled from individual
kernels of popcorn. Other procedures have been developed for the manufacture of porous, spherical particles [50]. Today, most analytical columns use spherical particles.

The silica used for HPLC columns before 1988 was usually derived from natural sources (water-glass solution) contaminated by various metals (e.g., iron, aluminum) that can increase its acidity. This often results in tailing peaks for basic compounds, poor column reproducibility, and other problems. These difficulties were largely overcome by preparing silica particles from the hydrolysis and polycondensation of pure tetraethoxysilane (TEOS). The latter, less-acidic silica is now referred to as type-B silica, in contrast to the older, less-pure, and more-acidic type-A silica. The first, widely used columns based on type-B silica were introduced by DuPont in 1988, and today most analytical columns use type-B silica.

One disadvantage of bonded silica is that it is unstable at both low and high pH. Particles of porous, spherical, graphitic carbon [51] provided one answer to this problem; the resulting Hypercarb columns were offered in 1994 by Hypersil. Another approach to pH-stable particles is the use of porous, spherical zirconia instead of silica [52]. The first widely distributed column of this type (ZirChrom PBD) was introduced in 1996. Similar, but less dramatic improvements in column stability can be achieved by changes in bonding chemistry (Section 1.3.2).

A quite different approach to HPLC columns was the development of so-called monoliths. Monolithic columns are cast as a porous, rigid cylinder by in situ polymerization and can be made from either silica or polymer. Several groups have contributed to their development, as reviewed in Ref. [53]. One advantage of monolithic columns is their greater permeability, allowing separations at lower pressures. Although the first monolithic column (SilicaRod, Merck) was introduced for sale in 2000, the use of these columns (as of 2016) has remained somewhat limited.

*Hybrid* particles are formed of an organic/inorganic structure, based on the reaction of TEOS and an alkyl triethoxysilane [54]. The resulting particles are stabler than their silica counterparts, with reduced acidity. Hybrid columns are therefore well suited for the separation of basic samples. The first hybrid column (XTerra, Waters) was offered for sale in 1999.

From 1970 to 1990, the preferred particle size gradually evolved from 10μm to about 3μm with a resulting improvement in separation speed. The use of very small particles requires an increase in the maximum operating pressure of the equipment (>6000 psi). Equipment for separations at much higher pressures was first described by Rogers et al. [55], later perfected by MacNair et al. [56], and eventually commercialized by Waters (*ultra*-HPLC or UPLC) in 2004. This enabled the use of 1.8-μm (Rapid Resolution, Agilent, 2003) and 1.7-μm fully porous particles (Acquity, Waters, 2004). A little later, the so-called core-shell (or superficially porous) particles (Halo, AMT, 2007) were introduced for use at pressures ≤6000 psi, but with similar performance as for smaller-particle columns and ultrahigh-pressure LC (UHPLC) systems. The latter shell particles consist of a nonporous core coated with a 0.5-μm layer of porous silica (total diameter 2.7 μm). Smaller diameter superficially porous particles (SPP) are also available today. Surface-coated particles of various kinds have played an important role in HPLC since the beginning; see the review of [57].
1.3.2 STATIONARY PHASES AND SELECTIVITY

Three stationary phases were used with surface-coated particles at the beginning of HPLC: an attached polymeric layer for ion exchange, a mechanically held liquid (liquid-liquid partition), and bare silica (adsorption). Although liquid-liquid partition was initially the most popular one, but the mechanically held liquid proved unstable, and operationally inconvenient. Various attempts were made to permanently bond an organic layer to a silica particle, with eventual success using a silicone polymer as the stationary phase (marketed in 1972 as Permaphase; DuPont). Subsequently, organosilanes were used as reactants; for example, (1.3)

\[
\text{Cl} - \text{Si} \left( \text{CH}_3 \right)_2 \text{C}_{18} + \equiv \text{SiOH} \Leftrightarrow \equiv \text{SiO} - \text{Si} \left( \text{CH}_3 \right)_2 \text{C}_{18}.
\]

(e.g., μBondapak, Waters, 1973). The latter approach has since been preferred for the preparation of RPC and other columns. One shortcoming of the original silane phases is their instability at both low and high pH levels, which can limit their application. The development of sterically protected stationary phases provided stability at a low pH [58]; the first column of this kind (StableBond, DuPont) was introduced in 1989. These columns use hindered silanes, where the methyl groups in the silane of Eq. (1.3) are replaced by bulky groups such as \( i \)-butyl.

Many other silanes have found use for HPLC stationary phases [30], for various purposes. The \( C_{18} \) group used initially has been followed by other ligands to yield phenyl, cyano, embedded-polar-group, and other columns. These column types can result in large differences in selectivity (Section 1.2.2), as well as provide other advantages (e.g., avoidance of stationary phase dewetting with highly aqueous mobile phases). For a review of column packings, including both the particle and stationary phases, see Refs. [50,59].

1.4 EQUIPMENT

Many of the innovations in HPLC equipment remain as proprietary company secrets or are buried in the patent literature. Most of the dates listed here are estimates based on personal knowledge, interviews, and (limited) patent information. Additional information on instrumentation prior to 1980 can be found in Ref. [60].

Early HPLC systems contained most of the same components used today, but with less-sophisticated execution. A reservoir, pump, injector, column, detector, and data collection system were required. Reservoirs most commonly consisted of laboratory glassware. Microfiltration of the mobile phase (solvents) was used. Solvent outgassing was not a big problem until on-line mixing and gradient elution became more important. At first, solvents were degassed prior to use by means of vacuum or heating, followed in the late 1970s by the more reliable helium sparging (Spectra-Physics [61]), and later in-line vacuum degassing.

Although complete HPLC systems were available from some vendors, many early workers built their own HPLC systems or purchased components and assembled HPLC systems from the “best” available modules. In the late 1960s and early 1970s, the Milton-Roy Mini-Pump formed the core of most home-built systems, as well as
some commercial units. This was a single piston pump with the stroke length adjusted to control the flow rate. It used a mechanical pressure gauge, whose Bourdon tube also acted as a pulse damper. Additional pulse dampening might be added with gas ballasts or additional Bourdon tubes. The Waters M-6000 (dual-reciprocating-piston) pump was introduced in 1972 [59,62] that rapidly became the gold standard. With two variable-speed, reciprocating pistons operating out of phase, pulsations and system volume were reduced, with piston volumes in the 100-μL range. Nester-Faust (later acquired by Perkin Elmer) and Varian took a different approach, with large (250–1000 mL) pistons, one for each solvent, driven by a screw drive. Depending on the solvent volume used per run, the pistons might need to be refilled after each run. Syringe pumps dropped from the market soon after a publication pointed out serious limitations in their use [63]: mobile phase compressibility could result in poor reproducibility of retention times, especially in gradient elution.

About 1976, Altex (later purchased by Beckman) introduced the Model 110A pump with a fast-refill feature [64]; its single piston could spend more than 50% of its duty cycle delivering solvent, thus reducing pump pulsations. A year or two earlier, Altex had introduced the Model 100 pump for operation at 10,000 psi, far exceeding the 6000 psi upper limits of other systems and foreshadowing today’s UHPLC systems. Another innovation in the late 1970s was Perkin Elmer’s tandem-piston or accumulator-piston pump, where the first piston feeds solvent to the second piston. This design reduced both pulsations and the number of required check valves from four to three (or, in some cases, two) and improved reliability—this feature is still common in many of today’s pumps.

The earliest gradients were generated with a single pump; the weak solvent A was placed in a beaker on a stir plate, and the strong solvent B was added to the beaker (by siphoning) as its contents were delivered to the pump. More reliable, on-line mixing was subsequently accomplished by controlling the relative flow rate of two solvents, each pumped separately by a dedicated pump to a high-pressure mixer. In the late 1970s, Spectra-Physics introduced a three-solvent, low-pressure mixing system [65] coupled with its patented helium degasser [61]. This was the first practical low-pressure mixing system that allowed the simultaneous use of up to three solvents. At about the same time, an alternative multisolvent design was featured in Varian’s 5000 pumping system [66]; this design introduced each of the three solvents directly into the pump head, minimizing bubble problems. These pumps also feature active inlet check valves, an innovation that eliminated most problems associated with these valves. As patents expired and licensing agreements were reached, the best of these features—low-pressure mixing, accumulator-piston pumps, and active check valves—became standard features on pumps from many manufacturers.

Sample introduction was a challenge for early HPLC users. For lower-pressure operation, a septum-type injector could be used, but these tended to leak and were difficult to use; stop-flow injection represented an alternative. The Waters U6K [67] was introduced in 1973, and allowed convenient and reliable injection into the flowing stream. The U6K also included an innovative flow-bypass channel that reduced the pressure shock when the valve was cycled, a common source of column collapse
with the less-robust columns in use at that time. At about the same time, Valco introduced six-port rotary injectors, a design that is now the industry standard. Rheodyne was formed soon after, and its injection valve [68] eventually became the industry leader. An automated valve inevitably led to an autosampler. One of the first widely used autosamplers, the Micromeritics model [69], used sealed vial cap that acted as a syringe plunger to deliver the sample. A needle was inserted through the cap, and the cap was depressed so as to displace sample into the needle and sample loop. Several companies later developed autosamplers that used a motorized syringe to draw samples from a vial into the loop of a fixed-loop injector. This and a needle-in-loop design [70] are the most common autosampler configurations today.

Although some of the early instruments (e.g., DuPont) included column ovens, many users did not consider column ovens necessary; others used hot water baths, heat tapes, or retired GC ovens to control the column temperature. Today’s ovens are designed specifically for HPLC, with either a resistance or Peltier heater both to maintain column temperature and preheat the mobile phase.

Data were first collected on strip-chart recorders; every user had a favorite technique to keep the paper from jamming or pens from clogging, either of which could mean loss of data. Manual quantification was the rule, using either peak height or area—the latter by triangulation, planimetry, or cutting out the peak from the paper and weighing it. Disc integrators were an innovation of the 1960s for GC and later provided some automation to the LC data collection process. Spectra-Physics and Hewlett-Packard pioneered digital integrators in the mid-1970s, which revolutionized HPLC data collection. In the late 1970s Nelson Analytical introduced software that could integrate peaks automatically, even with drifting baselines; this software became part of data systems sold by many manufacturers. With the introduction of the IBM Personal Computer in 1981, the death knell rang for stand-alone integrators. Peak integration and system control gradually migrated to this now universally accepted computing platform.

A recent advance in instrumentation is the development of UHPLC systems that exceed the traditional 6000 psi/400 bar pressure barrier; some systems (e.g., Shimadzu’s Nexera) offer pressures up to 19,000 psi/1300 bar. Waters introduced the UHPLC system in 2004, and many other manufacturers now supply competitive instrumentation. For optimal performance, these systems use sub-2-μm particles in short, narrow-diameter columns, which generate peaks of very small volume. Chromatographic band broadening due to noncolumn sources (especially injection, plumbing, detector configuration, and data processing) then became critical. The small volume design of UHPLC systems (and many newer HPLC systems) reduce, but do not eliminate, the band broadening problems that restricted the acceptance of <2-mm i.d. columns when first introduced in the 1980s.

### 1.5 DETECTORS

The first HPLC detectors were modified ultraviolet (UV) photometers with flow-through cuvettes [71,72]. A breakthrough for practical HPLC was the development
of a UV detector with a flow-through, 8-μL flow cell, initially developed by Picker Nuclear but popularized by Laboratory Data Control (LDC). By the early 1970s, commercial UV and refractive-index (RI) detectors became available, with many suppliers repackaging the LDC detectors. UV detection was convenient, because the 254-nm line of the low-pressure mercury lamp provided easy detection of aromatic compounds. With the addition of filters, phosphors, or zinc or cadmium lamps, wavelengths of 214, 254, 280, and 365 nm became accessible. A simple modification of the UV detector resulted in the fluorescence detector. Later in the 1970s, Varian and Schoeffel made the first widely used variable-wavelength detectors, enabling manual selection of any wavelength produced by a deuterium lamp (≈185–365 nm). The diode-array detector was introduced by Hewlett-Packard in the 1980s; it and the variable-wavelength detector are the most popular HPLC detectors today. At least two designs of RI detector were available during the 1970s: Fresnel and deflection instruments. However, RI has always been plagued by pump pulsations, temperature sensitivity, gradient incompatibility, and marginal detection limits; even so, RI is still a popular detector for size-exclusion chromatography (SEC). The evaporative-light-scattering (ELSD) and charged-aerosol detectors (CAD) are now far better choices as “universal” detectors than RI. Bioanalytical Systems introduced the electrochemical detector in 1974, an extremely sensitive detector for electroactive compounds central to neurochemistry.

The required reduction in extra-column peak broadening for UHPLC includes the detector, where the traditional 1.0×10-mm, 8-μL flow cell is no longer adequate. This problem has been solved by the use of internal-reflectance light-piping technology, resulting in 10-mm long cells with volumes of <500 nL.

The Holy Grail of HPLC detection in the 1970s was the conversion of universal or selective GC detectors for HPLC use. The near-universal nature of the flame-ionization detector attracted special interest. Techniques for removal of the solvent prior to detection included moving wires, mesh belts, and rotating disks [73]. Although commercial models were introduced, none was sufficiently reliable for routine use.

Other research or commercial detectors never reached widespread acceptance, for example, flame photometric, atomic absorption, dielectric constant, electron capture, heat of adsorption, spray impact, cholinesterase inhibition, nitrosamine detector, and electrolytic conductivity. The pursuit of an LC-MS (liquid chromatography-mass spectrometry) detector, analogous to GC-MS (gas chromatography-mass spectrometry devices, showed signs of hope when Vestal introduced a thermospray device [74] in the early 1980s. Although the latter detector exhibited great potential, it was not until Fenn’s development of the electrospray interface in the late 1980s [75] that LC-MS came of age as an HPLC detector. Today, LC-MS and LC-MS/MS detection is second only to UV in popularity and is growing rapidly as simplified systems are introduced and prices are dropping.

APOLOGIES AND ACKNOWLEDGMENTS

As with any condensed history, many significant events have been omitted (for additional details and different perspectives, see Refs. [1,3,13,59,76]). The present chapter also emphasizes
the use of HPLC as an analytical (rather than a preparative) technique. Although a very large literature deals with the theory of LC, in truth, only a small fraction of these studies have had much impact on the present use of HPLC. Similarly, we have not discussed the educational support provided by short courses, HPLC incubation centers in various universities, organizers of HPLC meetings, or the large number of HPLC books and review articles. These instructional aids have had a major influence on the continuing advance of HPLC as both a discipline and practice.

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REFERENCES


FURTHER READING