Pioneers of HPLC in Germany

A gallery of academic and industrial scientists in Germany who have been instrumental in making HPLC the analytical liquid phase separation technology it is today

The HPLC Symposium on High-Performance Liquid Phase Separation and Related Techniques has returned to Germany. After Baden-Baden in 1983, Hamburg in 1993, and Dresden in 2009, it will be held for the fourth time in 2023 at the Congress Center in Düsseldorf.

Since the inaugural meeting in Interlaken, Switzerland, in 1973, where the acronym HPLC Symposium was coined, it has been the home of key developments in HPLC. Many scientists have presented fundamentals of liquid phase separation, HPLC column preparation, stationary phase synthesis and characterization, applications for low and high MW compounds, molecules with high and low polarity, and ionic substances. They introduced equipment for high-pressure solvent delivery, sample injection, spectrophotometric detection, and coupling with mass spectrometry.

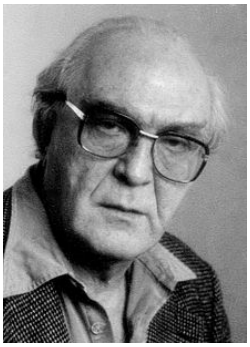
The founders of this world-renowned symposium in 1973 were Willy Simon, Jack J. Kirkland, Georges Guiochon, and Josef K. Huber. It continues for 50 years. Eminent scientists such as Csaba Horvath, Istvan Halasz, Heinz Engelhardt, John Knox, Klaus Unger, Barry Karger, Johan Poppe, Göran Schill, and many others have contributed to and shaped the field of HPLC to its exceptional standing.

Today's generation of (U)HPLC users may have forgotten these scientists and their role in developing HPLC. Even more, forgotten may be the contributions of German scientists and entrepreneurs who participated in the evolution and maturation of HPLC.

The Gallery of Honor presented here is intended to recognize the German pioneers who were internationally active in this field and to pay tribute to their contributions.

Prepared by: Gerard Rozing, Michael Schulte, Heinz Engelhardt, Frank Steiner and Markus Martin, and Oliver Gültzow.

István Halász 1922 -88 – Ultimate Limits and Practice of HPLC



After serving in the Hungarian army (1943/45), István Halász studied chemistry at the University Szeged, finishing a Ph.D. in Physical Chemistry in 1949. He continued his scientific career at the Institute of Physical Chemistry (with Prof. G. Schay) of the Technical University at Budapest, finishing 1954 his "Second Thesis on "the structural characterization of catalysts and adsorbents with vapor adsorption." He was promoted to the head of the "Gas Adsorption and Contact Catalysis" department at the Hungarian Scientific Academy in Budapest.

He came to Germany in 1956 and could start working at the Institute of Physical Chemistry at the University of Frankfurt/Main. He became a lecturer in 1961 and was promoted to Professor in 1964. Besides his academic work at Frankfurt University, he was the head of the "Gas Laboratory" at Scholven-Chemie AG at Gelsenkirchen (1957-1960).

In 1971 a research center for Analytical Chemistry was initiated at the University of the Saarland at Saarbrücken. With the focus on research on HPLC, the "Institute of Applied Physical Chemistry" has been established with István Halász as head of the department. He stayed at the Institute up to his retirement in 1987.

István Halász has been an internationally renowned scientist in the theory and practice of chromatographic separation techniques. He was invited as visiting Professor at the University of Nice (1968) and Northeastern University Boston (1970). His scientific work can be summarized under "Fundamentals in Optimization of Chromatographic Columns Performance." Initially, the improvement of capillary columns in gas chromatography led to the PLOT-Columns (Ph.D. thesis Cs. Horvath 1963).

Already in 1967, he switched to liquid mobile phases. Chemically modified silica has been introduced for the GC separation of small molecules (DURAPAK-Columns 1969). The derivatization via ester bonds was unstable in liquid chromatography. The optimization of reaction with silanes was a consequent development in 1969. His practical and theoretical work in HPLC has aimed to improve column efficiency via packing technologies, reduction of peak broadening in connecting tubes, the influence of column dimensions, particle diameter, etc. With his "pragmatical theory" of chromatography, he developed simple rules to evaluate the "limits" of HPLC.

Reproducibility, accuracy, and practical applicability of chromatography have been the center of his work; to transfer these values to his more than 50 students for their future way in science and industry has been his aim.

István Halász died in 1988. In 1990 by his last will, the István-Halász-Foundation was established at the University of the Saarland to further young scientists in Analytical Chemistry.

The Hungarian Society of Separation Science (HSSS) has awarded the Halász-Medal to renowned scientists in separation science since 1997.

(Contributed by Heinz Engelhardt)

Klaus K Unger, 1938 - 2020 – the Master of Porous Silica.

Figure 1: Photo was taken at HPLC 2007 Symposium (courtesy of Dr. Gerard Rozing)

Klaus K Unger was born in Zwickau, Germany, on June 16th, 1936. He studied chemistry at the Technical University in Darmstadt. He received his doctorate in 1965 at the Eduard-Zintl-Institute of Physical and Inorganic Chemistry. At the TU Darmstadt he started his research group, which reached a size of 15 Ph.D. students by the mid-1970s.

In 1976 he was appointed Professor of Analytical Chemistry at the Johannes-Gutenberg University in Mainz. He maintained his highly productive group at this university for 25 years until his retirement in 2001.

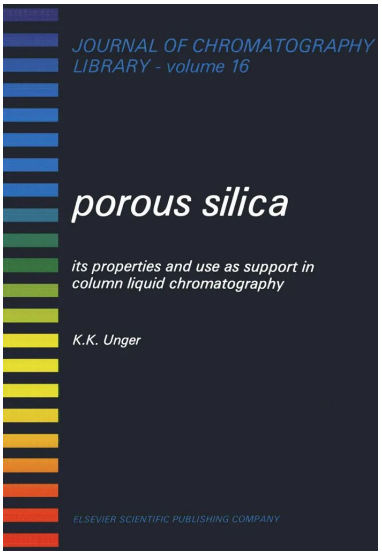
The Unger group worked on the synthesis of porous materials, mainly silica, that are used as adsorbents and catalysts. In addition, he worked on the functionalization and characterization of the surfaces of porous materials and especially on their application in chromatography.

From 1973 on, he established cooperation with E. Merck, in Darmstadt. The first two commercial products, Perisorb A and B, were based on the process developed by Klaus Unger in his laboratory to produce porous silica from tetraethoxysilane via poly(ethoxysiloxane). These were followed by the well-known LiChrosorb and LiChrosphere.

In 1973 Klaus Unger spent six months as a visiting scientist in Barry Karger ‘s laboratory at the Northeastern University in Boston. Together with him, Istvan Halasz, Bengt-Arne Persson, Johan Kraak, Heinz Engelhardt, Peter Schoenmakers and Wolfgang Lindner formed an outstanding group of postdoctoral fellows who in later times, became a network of pioneers in the field of HPLC. In Boston, Klaus Unger packed 1-3 µm silica into HPLC columns for the first time in his search for highly efficient chromatographic separation systems.

Klaus Unger´s first publications in the sixties demonstrated the need for highly efficient chromatographic systems[i],[ii]. Unger packed glass columns of 1 cm diameter and 195 (!) cm length with different silica gel materials varying in their pore diameter from 20-25 Å up to 500 – 700 Å. Polystyrene samples with a molecular weight of approximately 250.000 Da have been separated at a low flow rate of only 6 ml/hour.

Porous silica though was his life. In a landmark monograph he published in 1979, Unger has condensed all his knowledge on the structure of porous silica, the surface chemistry, the measurement of porosity, specific surface area, particle size, and size distribution, packing methods, surface modification and applications to ion exchange, and size exclusion chromatography. This book has become the bible of liquid chromatography on silica.



From the beginning of his academic career, Klaus Unger aimed to increase the separation power of chromatographic systems by influencing the A and the C-term of the Van Deemter equation. He optimized the A-term by using smaller and smaller particles (down to submicron particles), monodisperse instead of polydisperse particles, and spherical instead of irregularly shaped particles. He also worked on reducing the C-term in the van Deemter equation by using smaller particles (with shorter diffusion paths) down to the extreme of non-porous particles. The construction of uniform pores in an adsorbent, thus decreasing inhomogeneities in the pore structure.

After his retirement, Unger led a research group at Merck KGaA in bioseparation science in Darmstadt for another eight years until his final retirement in 2009.

Klaus Unger has been the author of over 400 publications, an author/co-author on 15 monographs, and co-editor of 17 Symposium Proceedings, the inventor of 55 patents on chromatographic materials and inorganic catalysts, and the supervisor of 125 Ph.D. students.

He has received several prestigious awards, including the A.J.P. Martin Award in Chromatography from the Chromatographic Society London (1993) and the American Chemical Society Award in Chromatography (1995). Unger was a member of the permanent scientific committee of the HPLC Symposium series and was the chairman and organizer of the symposium in Hamburg in 1993. He was the driving force behind the International Symposium on the Separation of Peptides, Proteins, and Polynucleotides (ISPPP) and the PREP HPLC series.

The work of Klaus Unger has shaped the world of HPLC in the seventies and eighties till today, modern UHPLC. He was truly a German giant and pioneer of chromatography.

Klaus died in 2020 at the age of 84 years.

(Contributed by Michael M Schulte)

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[i] Grundlagen chromatographischer Trennwirkungen des Silicagels, H. W. Kohlschütter, A. Risch, K. Unger, K. Vogel, https://doi.org/10.1002/bbpc.19650690918

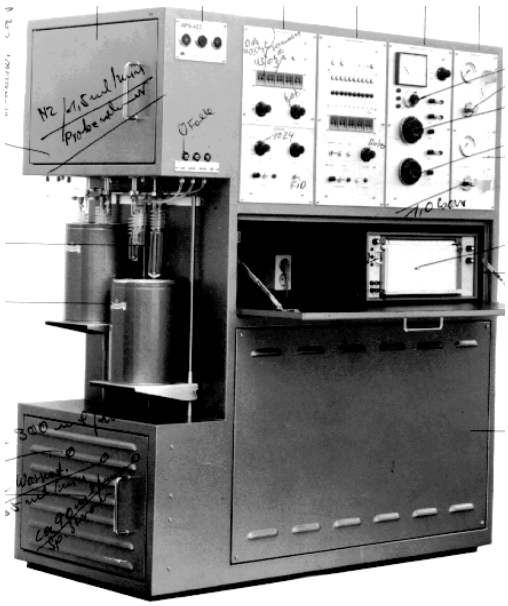
[ii] Chromatographische Fraktionierung und Trennung von Polystyrolen an Silicagel, K. Unger , K. Vogel and H. W. Kohlschütter, https://doi.org/10.1515/znb-1967-0104

Klaus-Peter Hupe – Scientist and Entrepreneur

Figure 2: Picture taken 2020.

Klaus-Peter Hupe was born in 1931 in northern Germany. He studied mechanical and process engineering at the Technical Universities of Braunschweig and Karlsruhe. He received his Ph.D. from the Institute of Thermodynamics at the Technical University of Karlsruhe in 1959 on "Heat and Mass Transport in Trickle Sheath Flow". Subsequently, he worked at the Technical University of Karlsruhe until 1962.

During this time, he was approached by Prof. Ernst Bayer and was asked to build a preparative gas chromatograph[iii]. This instrument was received with great enthusiasm by the users and created the demand for more systems.



This was the basis for the foundation of the company "Dr. Hupe Apparaten Bau" in Karlsruhe, which was dedicated to the design, manufacture, and marketing of preparative gas chromatography systems. In this instrument, a column packed with polyethylene glycol particles of 40 mm i.d. and 2 m length was used to collect fractions in mL volume fully automatically.

The late 1960s saw the emergence of the new field of liquid chromatography. With partner Dr. Busch, the “Hupe and Busch” company entered the field in 1972 by introducing the UFC 1000 Universal Liquid Chromatography System. This was the first fully integrated HPLC system on the market and the technology leader.

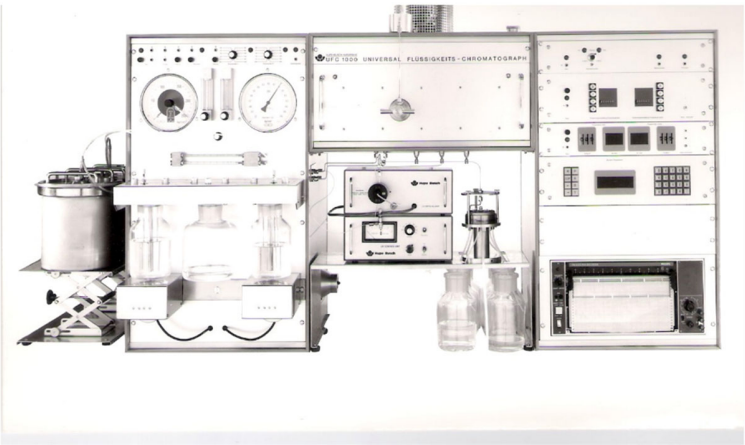


Figure 4:

With this system, Hupe & Busch company was acquired by Hewlett-Packard in 1973, and the system was marketed under the HP brand name 1010.

Dr. Hupe became general manager of the HP division and oversaw the development of the next generation of integrated HPLC systems, the 1080 series. With the company's relocation from Karlsruhe to the new site in Waldbronn, Dr. Hupe stepped down as General Manager to concentrate on separation science until his retirement in 1995. During that time, he continued to guide Hewlett-Packards HPLC instrumentation as a scientific advisor to the Waldbronn division, remaining very influential in product development, culminating in the prestigious HP 1090 series, which introduced narrow-bore HPLC to the market and made HP the technology leader in liquid chromatography systems into the late 1990s.

Dr. Hupe has published 50 papers on fundamental aspects of GC and HPLC and is an inventor on 11 patents. He has supervised two Ph.D. theses. He has been an associate professor at the Free University of Amsterdam since 1987.

He has been a member of the scientific committee of the HPLC Symposium for many years and was the chairman of HPLC 1983 in Baden-Baden.

Klaus-Peter Hupe is a scientist whose research brought HPLC from its infancy to maturity, and as an entrepreneur who shaped and established the industry and is considered the seed of Agilent's high-tech campus in Germany.

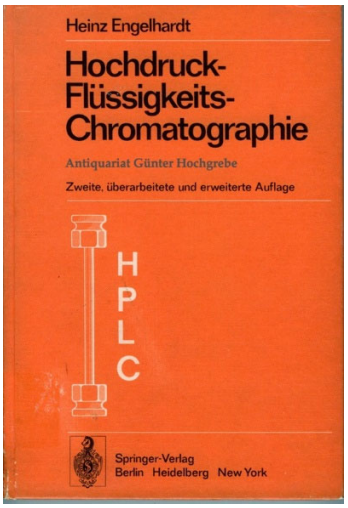
(Contributed by Gerard Rozing)

[iii] https://doi.org/10.1002/ange.19610731504

Heinz Engelhardt – Test for Characterization of HPLC Stationary Phases.

Born in Nuremberg in 1936, Heinz Engelhardt began his chemistry studies in 1954 at the University of Erlangen-Nuremberg, where he began his academic career in 1962 as a research assistant at the Institute of Organic Chemistry under Prof. Gerhard Hesse, an expert in the synthesis of natural products who introduced him to liquid-phase separations. Engelhardt received his Ph.D. in 1965 for his research on the influence of temperature on the adsorption chromatography of solutions. During his postdoctoral research, he spent almost 2 years (1969-1970) at the Barnett Institute of Northeastern University in Boston with Prof. Barry Karger followed by a guest-professorship in 1978.

After returning to the University of Erlangen-Nuremberg in 1971, he completed his habilitation in organic analytical chemistry with studies on support materials for liquid chromatography at high operating pressures. In the same year, he joined the Institute for Applied Physical Chemistry of Prof. István Halasz at the University of Saarland, Saarbrücken, where he remained after Halasz's retirement in 1987 until he founded the Institute for Instrumental and Environmental Analysis in 1994, which he headed until his retirement in 2002. He held several visiting professorships during his academic career, including at the Universities of Aix-en-Provence (France) and Innsbruck (Austria) in 1998/1999.

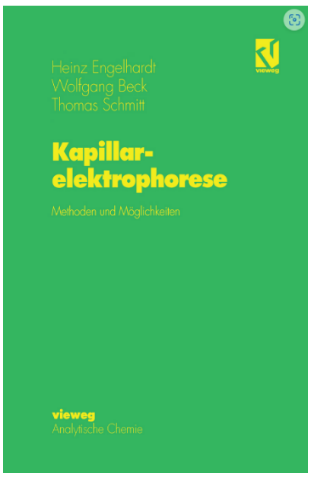


Heinz Engelhardt's main field of work has always been HPLC. His focus has ranged from pragmatic approaches to complex theoretical descriptions of LC, through stationary phase characterization, to developing stationary phase binding technologies for HPLC. His systematic studies of gradient elution in the 1970s and 1980s made the theoretical models of Giddings, Snyder, and others generally digestible. They led to practical user concepts for method development and scaling, laid down in a widely acclaimed monograph.

Another area in which Engelhardt made a significant contribution was the characterization of HPLC stationary phases with simple test compounds representative of hydrophobic, polar, or ionic molecular interactions. This resulted in the well-known **Engelhardt Test** as one of the most prominent HPLC stationary phase classification methods[iv].

Other research areas included synthesizing stationary phases for new selectivity in reversed-phase chromatography, ion-exchange chromatography, and enantiomeric separations.

After HPLC, Engelhardt's second main area of interest was capillary electrophoresis. In the 1990s, he investigated various surface modification technologies to actively modify and control the electroosmotic properties inside fused silica capillaries and suppress detrimental analyte-wall interactions. His involvement in CE applications ranged from analyzing inorganic ions with indirect detection to enantiomeric separations and the characterization of polyelectrolytes.



While at Saarland University, he supervised 97 doctoral students who continue to pass on his knowledge and work ethic in industrial and academic research facilities worldwide. More than 250 research publications to date testify to his extensive and multifaceted scientific creativity in liquid phase separation science.

In 1990, after German reunification, he and Prof. Werner Engewald founded the first series of meetings for young German separation scientists, bringing together the generations of a divided country to learn from each other and bridge the gaps left by 40 years of separation.

As an internationally recognized scientific leader in liquid phase separations, he has hosted several prestigious scientific conferences in Germany, twice the HPCE conference (in Würzburg and Saarbrücken) and the ISC conference (in Stuttgart), to name the most important.

In addition to publishing in peer-reviewed journals, Heinz Engelhardt has always aimed to communicate scientific knowledge to the everyday user of liquid phase separations, focusing on making it accessible to the German-speaking community. He published the first convenient guide to HPLC in the German language. Since its first publication in 1975, the book "Hochdruck-Flüssigkeits-Chromatographie" has gone through several editions and translations into several languages, including English, Russian, and Chinese. Among his many activities as a reviewer and consultant, he was editor of the journal Chromatographia for 13 years and a member of the Permanent Scientific Committee of the HPLC Symposium Series.

His dedication and commitment have been recognized with numerous research awards, including the A.J.P. Martin Award from the Chromatographic Society of Great Britain (1993), the Halasz Medal from the Hungarian Society for Separation Sciences (1997), the Clemens Winkler Medal from the German Chemical Society (2002) and an honorary doctorate from the University of Aix-en-Provence.

He will remain connected to the Engelhardt test protocol for characterizing stationary phases.

Contributed by Frank Steiner and Markus Martin

[iv] Chromatographic characterization of silica-based reversed phases, H. Engelhardt, H. Löw, W. Götzinger https://doi.org/10.1016/S0021-9673(01)83996-0

Herbert Knauer - Scientific instruments are his passion – especially HPLC systems

Dr. Herbert Knauer in his office, 2022 (Photo: Wikipedia)

Chemist, engineer, and entrepreneur Herbert Knauer was born on September 12, 1931 in Berlin-Karlshorst.

After graduating from high school at the age of 17, he began studying business administration at the Technical University of Berlin, because his preferred subject, chemistry, had too many admission restrictions (numerus clausus). He was able to change his major after a few semesters.

Herbert Knauer received his Ph.D. in 1958 from the Institute of Inorganic Chemistry at the Technical University of Berlin under Gerhart Jander with a thesis on 'Ion reactions in absolute diethyl ether as a solvent'.[1]

The freshly graduated doctor of engineering worked as a scientific assistant for the inorganic chemistry practical course program and remained at the TU until early 1963. During this time, he spent his afternoons and weekends in the kitchen at home - not as a hobby cook, but to develop technical solutions, such as a precision instrument for measuring the smallest temperature changes of 1/1000 degree Celsius, which was sensational at the time.

With the university's permission, Herbert Knauer and his wife Roswitha founded the company "Wissenschaftliche Gerätebau Dr. Ing. Herbert Knauer Gesellschaft mbH" in Berlin-Schmargendorf on October 1, 1962. After further development into so-called osmometers, temperature-measuring devices finally became a market success. KNAUER made a name for itself as the first company in Europe to manufacture osmometers for chemistry and medicine.

Inspired by a visit to a trade show in Bratislava in the early 1970s, Herbert Knauer had the idea of entering the HPLC instrumentation market. As a chemist, he recognized the great potential of this analytical technology, which was still in its infancy. The only competitor at the time was Waters, and in 1974 Herbert Knauer and his company became the first German manufacturer of HPLC systems.

The first generations of HPLC systems were bulky and difficult to use. Their components, such as pumps and detectors, were all in the same housing, making repairs or replacements difficult. Herbert Knauer saw this as a problem that needed to be solved. After discussions with chemists and researchers at various institutes in Berlin, he developed the solution: the first modular HPLC system. The stackable components were easily interchangeable, allowing different pump and detector

Modular KNAUER HPLC (Picture taken from a 1975 leaflet)

combinations to be easily configured and repairs to be easily performed. This design would soon become the standard for HPLC systems around the world.

Innovative solutions with a good price/performance ratio made KNAUER instruments known beyond the borders of Germany and opened up a large export market for the company. The personal participation of Herbert and Roswitha Knauer in important conferences and trade fairs around the world, where they not only presented the instruments but also discussed current developments with colleagues and users, also contributed to this success.

Herbert Knauer was always interested in further developing the instrumentation and HPLC columns. By 1987, KNAUER had dozens of stationary phases in its product line and manufactured separation columns with internal diameters ranging from 2 to 32 millimeters. Developments in this area also included column-filling equipment and capillary connection systems. The "Dynaseal" system, introduced in 1986, was groundbreaking in allowing safe, hand-tight connections for pressures up to 45 MPa.[2] Today, numerous "finger-tight" capillary connectors are on the market. In 1992, KNAUER introduced PC-controlled preparative HPLC systems that greatly simplified automated purification for chemical and pharmaceutical laboratories.

Early on, KNAUER also developed and produced instruments for competitors. The OEM business is an important pillar of the company. "The competition has always forced us to improve - we are very grateful for that," Herbert Knauer once said at an anniversary celebration. At the same time, KNAUER has left its technical mark on the industry by incorporating KNAUER technology in more instruments than one might think.

The open-mindedness towards new technologies is evident in the examples and extraordinarily high technical creativity that characterizes Herbert Knauer today. This way of thinking remains at the core of the company's philosophy. KNAUER received the Berlin-Brandenburg Innovation Award in 2021[4] and the German Innovation Award in 2022[5]. On September 10, 2021, the German Chancellor, Dr. Angela Merkel, visited the company and congratulated Herbert Knauer on his 90th birthday. She described the company as a "jewel in the German SME sector"[6].

Dr. Angela Merkel examining a production system for lipid nanoparticles (Photo: KNAUER)

Although Herbert and Roswitha Knauer handed over the company's management to their daughter Alexandra Knauer in 2000, Herbert's passion for science and technology remains unbroken; he is still a familiar face at the KNAUER headquarters, where he tinkers with components for HPLC systems.

(contributed by Oliver Gustow)

1) Herbert Knauer, Ionenreaktionen in absolutem Diäthyläther als Lösungsmittel, Berlin, T. U., F. f. allg. Ingenieurwiss., Diss. v. 10. Nov. 1958,
2) Chromatographia Vol. 22, No. 7--12, December 1986, p. 433
4) https://www.pharmaindustrie-online.de/management/knauer-mit-innovationspreis-2021-berlin-brandenburg-ausgezeichnet
5) https://www.laborpraxis.vogel.de/knauer-wird-fuer-loesung-zur-impfstoff-produktion-ausgezeichnet-a-1116097/
6)https://www.bundesregierung.de/breg-de/aktuelles/pressestatement-von-bundeskanzlerin-merkel-bei-der-knauer-wissenschaftliche-geraete-gmbh-am-10-september-2021-1959124