# Henry (Hank) M. Fales: Pioneering Adventures in Medical Research with Mass Spectrometry

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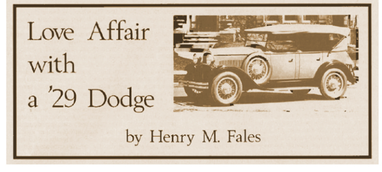
**Henry Fales** was born on February 12th, 1927 in New York City. Upon graduation from high school in 1944, he enlisted in the Navy Air Corp for a two year tour of duty. After his service in World War II, he resumed his education, earning a Baccalaureate degree at Rutgers in 1948 followed by a Ph.D under the tutelage of R. A. Barnes, an organic chemist, in 1953. His work career began at the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH), in Bethesda, Maryland. There he worked under E. Horning and W.C. Wildman in the Laboratory of Chemistry. Although Fales' intention was to take a job in industry after a short stint at NIH, he found the work with Wildman both challenging and rewarding. The lab specialized in structure determination of alkaloids which were of particular interest as potential candidates for new drugs. The analytical tools available when Fales started at the Laboratory of Chemistry were traditional wet chemical methods, coupled with combustion analysis, and infra-red and ultra-violet spectrophotometry.

### Pioneering Adventures with a Classic Car

Hank Fales had many interests outside of science. Besides devotion to his family, he was a pilot, an avid fisherman, and lover of classic automobiles. The latter resulted in automotive escapades when he tried to keep a 1929 Dodge running that he had purchased with the mustering-out funds from his Navy service. In 1986, he fondly recalled events with the classic car that 40 years of distance from the experience had mellowed in a publication in Skinned Knuckles. [1]




For the next decade, Fales, along with Wildman and later Robert J. Highet, performed structure determination with these tools on several dozen alkaloids, producing almost 40 papers. However, Fales was always on the lookout for any analytical tool that he could effectively used in his research. In 1960, he and his colleagues were among the first to use gas chromatography in their alkaloids studies. [2]

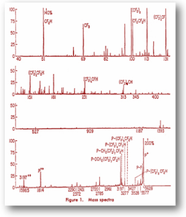
Several years later, the group studied an alkaloid, amaryllisine, whose structure they could not reconcile with the information from the analytical tools at their disposal. In part, the difficulty related to the miniscule amount of material they were able to extract compared to the amount needed – typically five milligrams – for reliable combustion analysis. About this time, Fales and his colleagues became aware of alkaloid research being conducted at the Massachusetts Institute of Technology by Klaus Biemann using mass spectrometry. So it was natural to see if mass spectral analysis of amaryllisine could help solve the problem. The task was given to one of Biemann's graduate students, Alma Burlingame, who performed both low and high resolving power mass spectral analysis of the compound; providing Fales with the key piece of information to complete the structure determination. It is characteristic of his generous, and helpful, character that Burlingame was listed as the first author on the publication. [3] This experience clearly demonstrated the utility of mass spectrometry as an analytical tool for their research; it required orders of magnitude less sample and provided much more useful information than combustion analysis. Fales immediately began the process of purchasing instruments at NIH.

Fales and Highet at the AEI MS-902 mass spectrometer

### Pioneering Mass Spectrometry at NIH

Fales chose the Associated Electrical Industries (AEI) MS-902, a high resolving power double focusing pseudo-Nier-Johnson geometry mass analyzer with electrical detection. This was completely different from the instrument in Biemann's lab, a Consolidated Engineering Corporation (CEC) 21-110 double-focusing Mattauch-Herzog geometry mass analyzer with photoplate detection. In addition, with several years of gas chromatography experience in Fales lab, he also arranged for the purchase of an LKB-9000 combined GC-MS instrument.

### Pioneering High Mass Range



The specifications of his new MS9 instrument indicated that it had a mass range of 4000 at reduced accelerating potential. Of course, to use that mass range, a calibration compound was needed. An Australian colleague, Ian Brown, furnished Fales with a heavily fluorinated compound with a molecular weight of 3628 to use as a mass calibrant. Shortly thereafter, he published the spectrum in Analytical Chemistry [7]; quite possibly the highest mass mass spectrum of a compound at that time.

Fales quickly realized the analytical power of mass spectrometry but just as quickly learned of its limits. Electron ionization (EI); the only viable ionization method then available, was not suitable for many of the compounds of interest at NIH. Chemical ionization (CI) was reported [4] in 1966 and Fales saw how it could be put to good use in his structure determination research. In short order, he contracted with Scientific Research Instruments Corp (SRI) to have Marvin Vestal build a CI source for his MS-902 [5]. This led to a pioneering paper [6] promoting CI as a means of studying biological compounds in the biological and biomedical communities.

## *Pioneering in the Amazon*

In 1976, the opportunity to take a field trip to the Amazon was too much for the adventurous Fales to resist. The goal was to perform a limited examination of many of the natural products native to the area before they were lost. His job was to serve as the mass spectrometrist aboard the R/VAlpha Helix using an instrument on loan from LKB for the research. A faulty instrument ground led to some exciting pyrotechnics forcing Fales and an associate to assume the roles of instrument repairmen in the middle of the Amazon. His collaboration with Murray Blum both before and after the trip led to over two dozen papers related to the biology of insects, their toxins and venom.

### Pioneering in Drugs of Abuse

Fales and his coworkers were in the lead in the use of mass spectrometry to identify drugs in overdose patients in the emergency room in the early '70s. Fales collaborated with his neighbor Norman Law, and was frequently called into the local hospital in the middle of the night. While combined GC-MS had been brought to bear on the problem [8], Fales and his group explored means of speeding the analysis using isobutane CI. They showed that CI spectra of a wide variety of drugs were simple and could be used to indicate the presence of drugs in a mixture extracted from body fluids [9]. When speed of analysis was of the essence, this analytical approach was used to good advantage.

When plasma desorption ionization was first described by Ron Macfarlane [10], Fales realized the utility of the new ionization technique and, in 1980, arranged for Macfarlane to build an instrument at the NIH Labs. It was used to produce over a dozen papers in the following decade on a wide variety of compounds of biological interest. With these tools, Fales and his group conducted research in natural products, biochemistry, insect pheromones, and protein structures, resulting in 300 publications.

Not content to restrict his interests to using mass spectrometry as a research tool, Fales was instrumental in creating a library of reference mass spectra for computer search routines. Furthermore, he assisted in making access to the library easy for researchers throughout the country, providing a means of searching through almost 9000 EI spectra over a teletype and standard landline connection. Primitive by today's standards, it was state of the art at the time; providing a very useful service at a low cost. Today, that modest initial collection is now the NIST/EPA/NIH Mass Spectral Library with almost 200,000 EI spectra, as well as 293,000 Kovats retention index values for 44,000 compounds.

Fales was not only a pioneering scientist, but he also interacted with and mentored other scientists from a variety of backgrounds. His publications have over 500 co-authors; both inside NIH and from around the world. Among those who benefited from having Fales as their mentor are G. W. A. (Bill) Milne, Lewis Pannell, Emily Boja, Robert Mason and Simone König. His most highly cited works evidence his scientific diversity and curiosity, from the identification of osmotically active organic solutes in kidney medulla; to the identification of a female moth sex-pheromone neuropeptide; and the construction of a simple device for preparing ethereal diazomethane. He was a solid citizen of the mass spectrometry community, volunteering his time and energy to serve in a variety of offices on the Board of Directors of the American Society for Mass Spectrometry for eleven years. He was Secretary for three years; two of which were before professional help was hired to deal with the increasing burden of Society business. He functioned as a catalyst for idea exchange among scientists in the Washington DC area, when he co-founded the Washington Area Mass Spectrometry Discussion Group. Hank Fales was a meticulous scientist with a generous personality; an outstanding mentor, and an adventurous investigator anxious to explore new ideas and fields. He had an impish smile and a love of life that endeared him to all who had the good fortune to make his acquaintance.


**1927** Born in New York on February 12th

**1927** Aston delivers Bakerian Lecture on "A New Mass Spectrograph and the Whole-Number Rule"

**1943** Washburn, Harold Wiley & Rock publish results from first commercial mass spectrometer

**1944** Trained for Navy Air Corps at Annapolis

**1944** Mattauch in Germany reports a "New Method for Measuring the Relative Abundances of Isotopes"

**1946** Enrolls at Rutgers University

**1946** Stephens describes "A Pulsed Mass Spectrometer with Time Dispersion" in Physical Review

**1948** Bachelor of Science in Chemistry from Rutgers

**1949** Bennett publishes "Radiofrequency Mass Spectrometer" in Journal of Applied Physics

Washburn & Berry patent 180 degree Mass Spectrometer

**1953** PhD in Organic Chemistry from Rutgers and takes position as instructor

Joins National Institutes of Health

**1954** William Wiley patents Time-of-Flight Mass Spectrometer

**1957** Reports nine major IR bands associated with methoxy, ethoxy and methylenedioxy groups

**1960** Co-author "Separation of Alkaloids by Gas Chromatography"

**1962** Biemann publishes "Mass Spectrometry: Organic Chemical Applications"

**1964** Mass spectrometry resolves problem in structure of amaryllisine

**1966** Identifies compound in Balsam Fir that acts as a juvenile hormone in *Pyrrhocoris apterus*

**1966** Munson & Field describe "Chemical Ionization Mass Spectrometry" in Journal of the American Chemical Society

**1969** Co-author "Chemical Ionization Mass Spectrometry of Complex Molecules"

**1971** Co-author "Identification of Dangerous Drugs by Mass Spectrometry"

**1971** Munson & Field patent Chemical Ionization Source

**1972** Co-author "Interactive Mass Spectral Search System"

**1973** Reports simplified method of preparing ethereal diazomethane

**1975** Co-author "Comparison of mass spectra of some biologically important compounds as obtained by various ionization techniques"

**1976** Macfarlane & Torgerson describe "Californium-252-plasma desorption time-of-flight mass spectrometry"

**1976** Amazon field trip on R/V Alpha Helix

**1980** Blakley & Vestal publish "Combined liquid chromatograph/mass spectrometer for involatile biological samples" in Clinical Chemistry

**1983** Publishes "Californium-252 Plasma Desorption of Natural Products"

**1986** Hillenkamp reviews "Laser Desorption Mass Spectrometry"

**1986** Reports osmotic activity of organic solutes in rat & rabbit renal medullas

**1988** Fenn ignites 'electrospray revolution' with papers at 36th ASMS Conference in San Francisco

**1989** Reports neuropeptide hormone that regulates sex-pheromone in female moths

**1991** Hillenkamp & colleagues publish "Novel method for matrix-assisted laser mass spectrometry of proteins" in Analytical Chemistry

**1999** Reports PTP1B via glutathionylation of the active site cysteine 215

**2001** Reports reversible glutathionylation regulates actin polymerization in A431 cells

**2009** Co-authors "Synthesis, Activity, and Pharmacophore Development for Isatin-β-thiosemicarbazones with Selective Activity toward Multidrug-Resistant Cells"