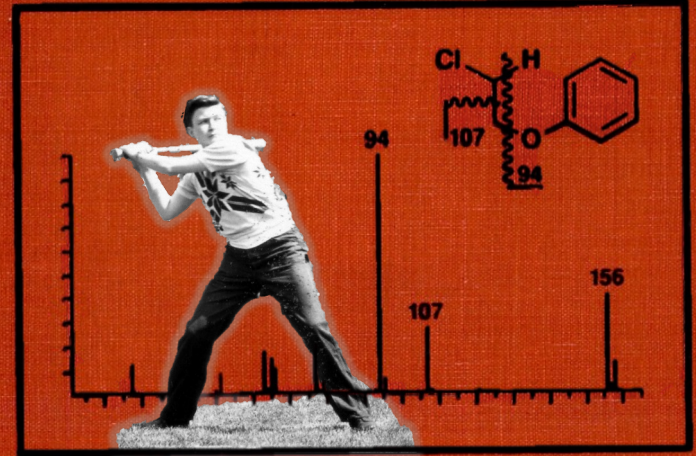




Fred Warren McLafferty: A Lifetime of Mass Spectrometric Work (& Play)
May 11, 1923 – December 26, 2021

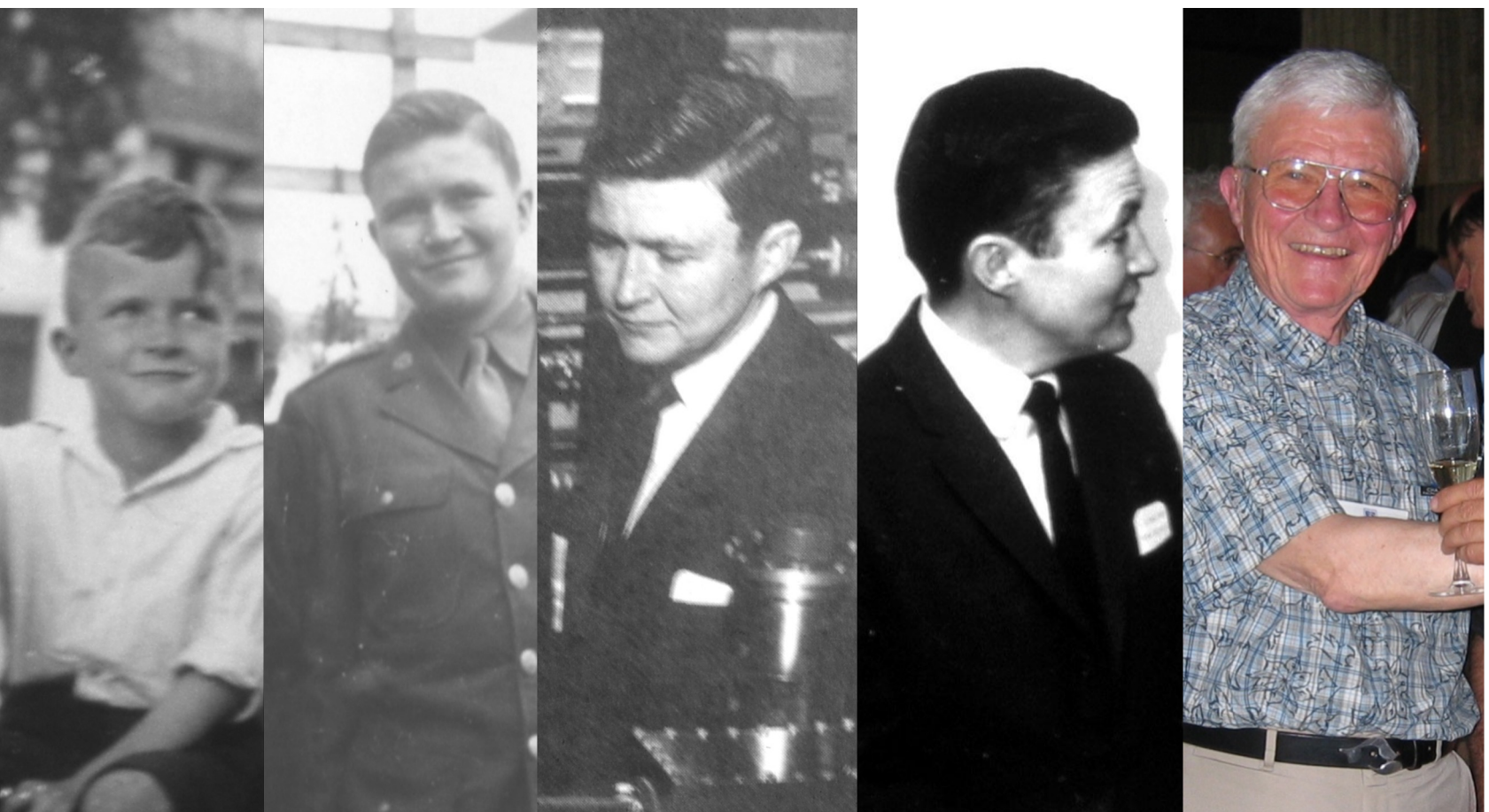
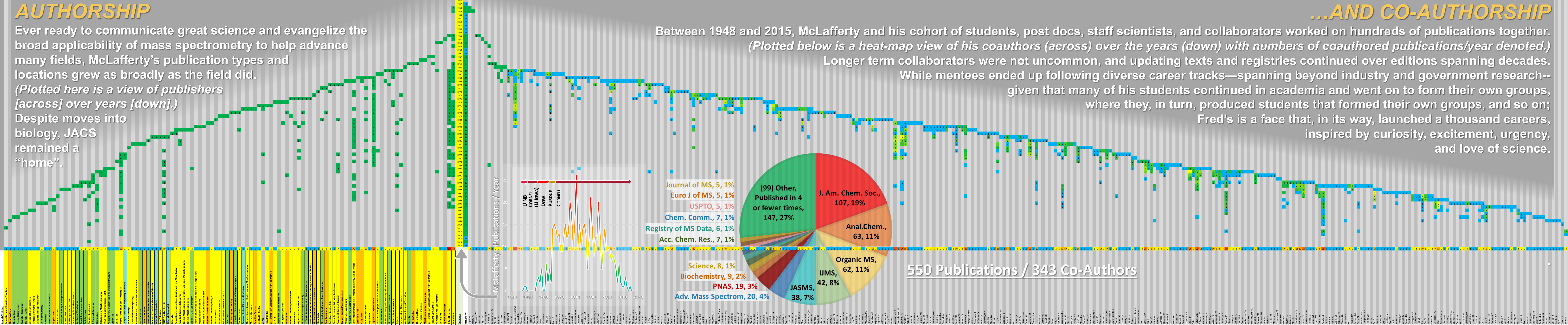


AUTHORSHIP

Ever ready to communicate great science and evangelize the broad applicability of mass spectrometry to help advance many fields, McLafferty's publication types and locations grew as broadly as the field did.

(Plotted here is a view of publishers [across] over years [down].)

Despite moves into biology, JACS remained a "home".



INDUSTRY AND ION SOURCES

Though he initially went to interview in organic research at Dow, he had a fortuitous earlier-in-the-day interview in their Spectroscopy laboratory, specifically in Mass Spectrometry, which seemed interesting enough to become a life turning point. Now he was a mass spectrometrists!

Industrial research was *laissez faire* at the time, directed by committee but with great freedom, putting responsibility in researchers to rise to compete. Fred ended up in charge of mass spectrometry and gas chromatography: getting new instruments, improving the instruments they had, and finding correlations of spectra.

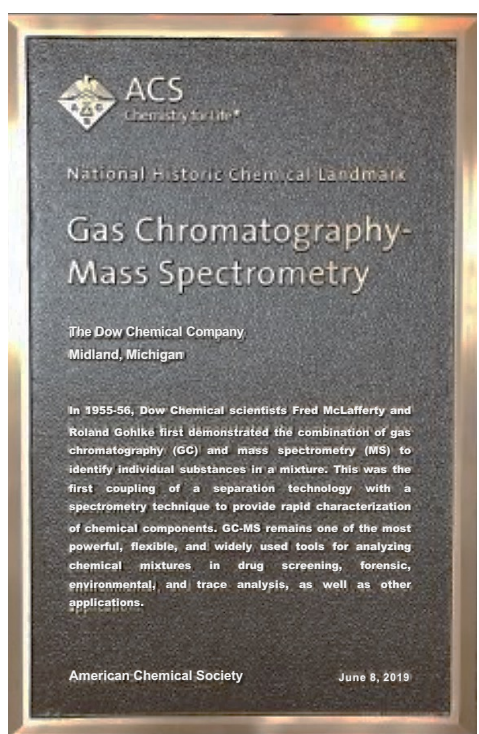
Part of that improvement was the development of the first GC/MS. Coming back from a Gordon Conference with a notebook full of notes on how to make a GC, Fred engaged colleague Roland Gohlke in the project. Together they overcame issues of making their own columns—Roland loved Tide detergent, an economical stationary phase—devised valving to sample small amounts of material from the GC without altering retention times, and coupled it to a ToF MS at Bendix, for 10k full spectra/s MS analyses in the photographing-oscilloscopes era of spectra production. These first GC/MS results were presented at the 1956 national ACS meeting, with a more polished first journal article about the work in *Analytical Chemistry* in 1959.

As industry became more enamored of basic research laboratories, Fred ended up being the first Director of the Dow Chemical Co. Eastern Research Lab in Framingham, MA. He would periodically use consultants to get perspective to assist keeping research moving in the right directions.

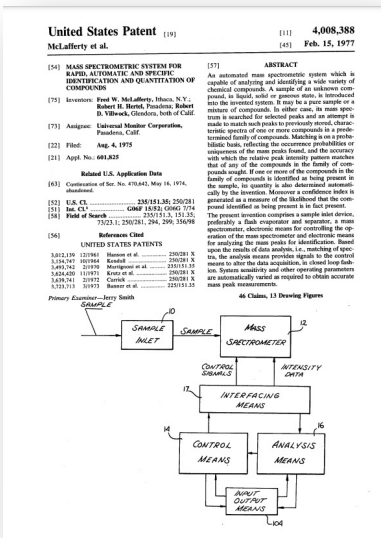
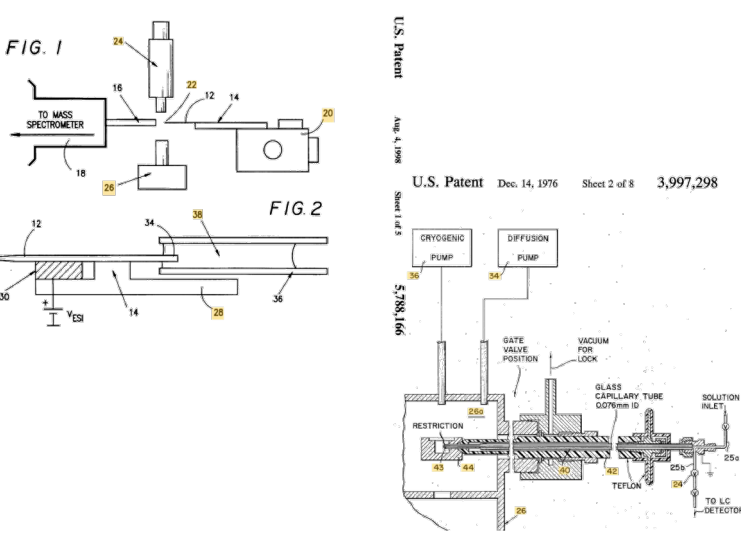
DATABASES

Fred noted there was not a better infrared lab in the world than at Dow. As he was competitive by nature, he noted they'd bring in samples from any place they could to build their IR spectral database whenever their instruments had idle time. Fred adopted this workflow, grabbing drawers full of their compounds and building his own broad reference database for organic compounds. The American Petroleum Institute's "Database of Mass Spectra" at the time was both more standardized and controlled and focused on hydrocarbons, leading to the spectral 'quality' parsing that led to Fred's participation on a "Subcommittee for Uncertified MS Data" as part of ASTM Committee E-14 on Mass Spectrometry, a precursor to ASMS. This qualitatively useful data was added to the database as Gohlke was recruited from Midland to Framingham to contribute more effectively, making a book with 2000 spectra adding to the API Database of 2500. With students and collaborators over the years since, that database grew to over 600,000 entries.

Looking again toward how the infrared spectroscopy scientists at Dow were searching their databases, where peaks were put onto punch-cards and a switchboard used to sort and select the appropriate spectra, the mass spectral group also made cards for spectra. In later times at Purdue and Cornell with Rengachari (Babu) Venkataraghavan, the computerization of these data—bypassing photoplates—and developing a Self-Training Interpretive & Retrieval System (STIRS) and a Probability Based Matching (PBM) System lay the groundwork for a lot of future global MS analysis, though he insisted that "YOU identify the compounds, not pattern matching programs".



60 years after the initial GC-MS publication, the American Chemical Society honored the innovation with a National Historic Chemical Landmark in a ceremony in Midland, Michigan, June 8, 2019.



FRAGMENTATION, FUNDAMENTAL CHEMISTRY AND REARRANGEMENTS

Having that collection of spectral punch cards from the initial MS databases gave Fred the opportunity to look for correlations in fragmentations where 'extra' hydrogens were showing up in enough organic compounds to seem like a trend to investigate. It was his 1959 publication on the rearrangements in mass spectrometry (specific and non-specific in the context of odd- and even-electron ions), as well as the mechanism for that particular cleavage in an assortment of compounds, that led to the rearrangement being named after him by Carl Djerassi. Fred was quick to acknowledge that the trend had been noted with some specific examples a few years earlier by his pal Tony Nicholson's non-charged radical-based photochemical rearrangement, published in 1954, as well as by a group from Kodak in a JACS paper in 1951. Nevertheless, Fred's contributions to the field continued to extend the early work on basic gas-phase ion chemistry. Doing some of the first MS/MS for structure determination with metastable ions and the first collisionally activated dissociation at Purdue, later this work wrapped around to things like neutralization reionization and electron capture dissociation; and to apply fundamental fragmentation understanding to the broad characterization of biomolecules at Cornell.

BOOKS & LITERATURE

The "Interpretation of Mass Spectra" book (1966, 1973, 1980, & 1993 editions) came out of short courses that were taught for the American Chemical Society. (Fred noted "The easiest way to write a book is to teach courses!") Whereas these books focused on electron ionization (EI), the applicability of odd electron ions falling apart based on radical chemistry remained relevant through the era of Electron Capture Dissociation (1998). The royalties from these books, along with those from *Mass Spectrometry of Organic Ions* (1963), *Mass Spectral Correlations* (1963, 1982), *Advanced Analytical Chemistry Instructions*, 1966-1975, and *Tandem Mass Spectrometry* (1983), were used to supplement funding for the lab's work in later years. While Cornell did patent some of the interfaces, most work was openly kicked around at meetings as Fred thought nothing was more important in the evolution of mass spectrometry.

APPLICATION SHIFTS

Fred often expressed the broad sentiment that **if you can't do it with Mass Spectrometry, it might not be worth doing**. Arguably, this may have led to some developments in ways to apply mass spectrometry. Approaching work from a perspective of instrument and method development while being an excellent organic chemist—even if he might have denied it—Fred's work spanned fundamental ion chemistry through to applications in biology. In the *top left* time resolved view of the places he published work, it is notable that there were more green/biological applications papers in the later era of work; however, in the pie chart, breaking the body of work down by actual number of publications in each area, it is notable that even with the biological shift in later years, the analytical and mass spectrometric angles of the chemistry still dominate the overall.

Generally brave about transcending disciplines, Fred would note that one cannot be an expert in everything, but one can find great collaborators. He was a doer: when things didn't work, he could and would pivot to something else and was ready to adopt new technologies to keep moving forward. He would note that "John Fenn saved my career with electrospray ionization and Comisarow and Marshall saved my career with FTMS" in discussions about how various methods really expanded how large molecules could be introduced and analyzed in instrumentation. He remained competitive: footnoting experiments to be done and generating nomenclature that became widely adopted, like "Top-Down" and "Bottom-Up" in protein characterization contexts.



ACADEMIA AND MENTORSHIP (1964-2016)

Fred appreciated that supervisors continuing to steward their exploratory research as it progressed was a core reason why academic laboratories could excel beyond industrial. However, he impressed upon both students (and strangers) the importance of being excellent in science *wherever one was*, finding or making or fighting for the time to do the kinds of research they wanted to do. He noted, **the most important thing about research is that you love doing it!** There was a *family comes first* attitude and readiness to sacrifice what was necessary to ensure both he and students could navigate multi-body timelines before (or while) having fun doing the science that felt like a mission in life in collegiate environments.

About personal matters, Fred was always helpful; generous with time and even periodically covering unexpected bills. He helped many students become citizens, in some cases lobbying congressional representatives on both sides of the aisle. His students became family, helping one another with research needs (informational and chemical) years after graduation, and seeking each other out at conferences. Fred emphasized the importance of conferences as places where he could talk to people and have ideas. Despite being a very competitive presence in the field, he was still periodically inclined to reach out and commend authors of papers he liked, making folks think: **Would Fred Learn Anything from This?**

Let's do the best we can do with what we have. But it has to be the best.

Fred had high standards and was straightforward with criticism. He seldom pulled punches but found arguments and follow-up discussions important. He was meticulous even as a big picture person. Group meetings were a type of combat: *if you argued with him, you were fine; if you argued with him with data, you were golden; if you argued with him and you were wrong and you didn't have data, you were dead; that was the way he was*. And it was clear that was how he believed science worked best: **you argued it out**. And he would apologize if you were proven right, *particularly* if the reviewers agreed with you. He was sharp and had an infectious excitement about the projects and the data and when things didn't fit together perfectly, he found that the most fun of all.

Sometimes you figure it out, sometimes you figure it out wrong. ...Then it's 2 publications!

RECOGNITION

Fred revolutionized the field and inspired the scholarship of peers and students alike. Though "countless" feels like a lazy word, he received no small amount of recognition for his work over his life, even for his conduct in battle in advance of the bulk of most of his science. A non-comprehensive list includes:

A Purple Heart/Combat Infantry Badge
5 Bronze Star Medals for Valor
Presidential Unit Citation

Nichols Gold Medal (ACS 1984)
J. J. Thomson Gold Medal (Intern. MS Soc. 1985)
Univ. Naples Gold Medal (1989)
Robert Boyle Gold Medal (Roy. Soc. Chem. 1992)
J. M. Bijvoet Medal (Utrecht Univ. 1997)
J. Heyrovsky Medal (Czech Acad. Sci. 1999)
G. Natta Gold Medal (Italian Chem. Soc. 2000)
Torbern Bergman Medal (Swedish Chem. Soc. 2001)
Lavoisier Medal (French Chem. Soc. 2004)

Hon. DSc degrees: Univs. Nebraska (1983), Liege (1987), Purdue (1995).

ACS Award in Chemical Instrumentation (1972),
Spectroscopy Soc. Pittsburgh Award (1975)
ACS Award in Analytical Chemistry (1981)
Oesper Award (Cincinnati ACS 1985)
Anachem. Award (1985)
S. C. Lind Award (E. TN ACS 1986)
W. L. Evans Award (Ohio St. U. 1987)
Pittsburgh Anal. Chem. Award (1987)
ACS Award in Mass Spectrometry (1989)
Pioneer Anal. Instr. (1994)
Chem. Pioneer Award (Am. Inst. Chemists 1996)
Disting. Contrib. Mass Spectrom. (ASMS. 2003)
Pehr Edman Award (Intl. Assoc. Protein Struct. Anal. Proteomics 2006)

