John Fenn

(1917–2010)

Chemist who enabled mass spectrometry to weigh up biology.

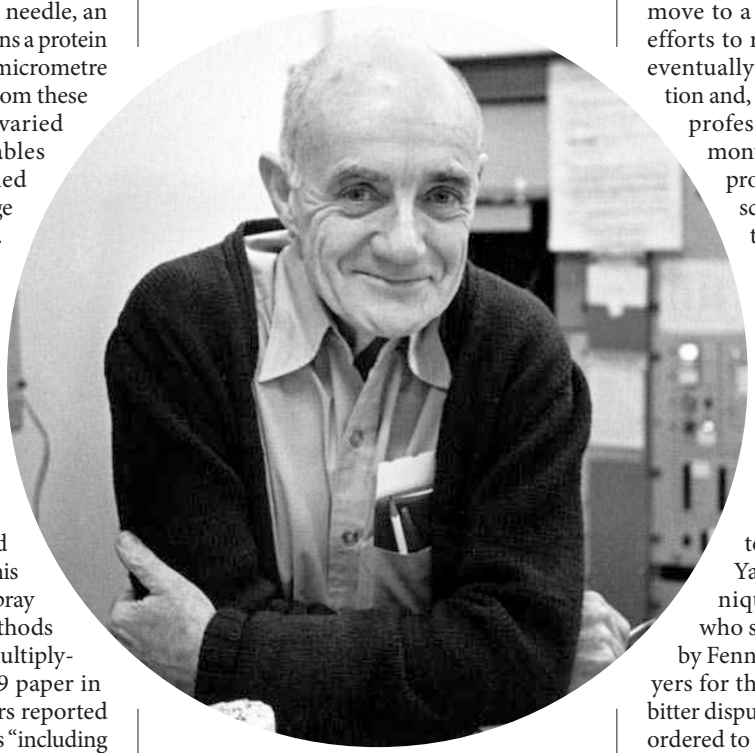
John Fenn shared the 2002 Nobel Prize in Chemistry with Koichi Tanaka and Kurt Wüthrich for his development of electrospray ionization, which, coupled with mass spectrometry, revolutionized the identification and structural analyses of large biological molecules. With characteristic wit, Fenn described the discovery as having given "wings to molecular elephants". He died on 10 December 2010, aged 93, following a fall.

Electrospray ionization enables intact proteins to transition effectively from the solution to the gas phase. By applying a high voltage (2–3 kilovolts) to a fine needle, an aerosol spray is produced that turns a protein solution into droplets in the submicrometre range (0.1–0.4 micrometres). From these fine droplets, protein ions of varied charges are formed. This enables protein masses to be determined from the series of mass-to-charge peaks in the mass spectrum. Many ions with different charges enable many measurements, so phenomenal accuracy can be achieved in the mass determined for the intact protein.

This development opened up new areas of research in the 1990s, including proteomics. For example, the molecular mass of a 17-kilodalton protein, such as myoglobin, could be measured with an error of less than 0.01%. This was not possible prior to electrospray because existing ionization methods were incapable of producing multiply-charged protein ions. In a 1989 paper in *Science*, Fenn and his co-authors reported obtaining spectra for biopolymers "including oligonucleotides and proteins, the latter having molecular weights up to 130,000, with as yet no evidence of an upper limit". This turned out to be a prophetic statement.

More than 20 years on, it is now possible to obtain well-resolved electrospray mass spectra of intact ribosomes and viruses, with molecular masses of several million daltons. At the time of the initial reports it was not clear whether non-covalent interactions could be preserved within these gas-phase protein complexes, let alone any of their three-dimensional structure. It is now clear that protein–protein interactions both survive the phase transition and retain aspects of their native structure. As a consequence, electrospray has spawned another unexpected field: gas-phase structural biology.

Fenn was born into a middle-class family in New York City in 1917, later moving with his family to Kentucky. He received his bachelor's degree in chemistry in 1937 from Berea College. The assistant registrar at Berea, Margaret Wilson, was ten years his senior; he married her in 1939. With Margaret providing the 'fellowship', in 1940 Fenn received his PhD in physical chemistry from Yale University in New Haven, Connecticut, for work on the properties of electrolyte solutions.



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After periods at industrial chemical companies, including Monsanto, Fenn joined a start-up company, Experiments, Inc., in 1945. He contributed to a large effort by the US Navy to develop a ramjet-powered anti-aircraft missile. The missile depended on pressure from high-speed flight to compress air enough to allow it to expand after combustion to provide thrust. Supersonic flight velocities were required to achieve sufficient thrust — igniting Fenn's interest in supersonic flows. Continuing this research, he moved in 1952 to Princeton University in New Jersey as director of Project SQUID, a jet-propulsion programme funded by the US Office of Naval Research.

In 1962 John returned to Yale. Here he remained until 1987, doing the majority of his Nobel-prizewinning work. In the 1960s, Fenn was interested in combustion, flame theory and stabilizing flames in high-speed flows. He decided that the way to study flame reactions was to do molecular-beam experiments. By the 1970s, he had realized that one way to get bigger molecules into the gas phase was to take a solution, disperse it, and let the solvent evaporate. So began his earliest electrospray experiments.

Meanwhile, he had to fight off a mandated move to a smaller laboratory space and efforts to retire him as he passed 70. He eventually conceded his space and position and, after a short spell as an emeritus professor, moved to Virginia Commonwealth University as a research professor in 1994. He believed that science should above all be fun and that when it ceases to be so you should give up. Fenn never gave up, continuing his research and coming into the department almost every day until just a few weeks before his death. His final paper on the mechanism of electrospray was published when he was 90.

In 2005, Fenn lost a dispute with Yale over the patent rights to electrospray. He claimed that Yale had abandoned the technique and that he was the person who saved it. A personal patent filed by Fenn was deemed 'civil theft' by lawyers for the university. After a decade of bitter dispute, and a failed appeal, Fenn was ordered to pay costs and damages totalling more than US$1 million.

Electrospray mass spectrometry continues to open doors — even in preparative mass spectrometry, where proteins and their complexes can be recovered and visualized after their flight in the gas phase. But Fenn's true legacy is the modesty and capacity to inspire that leave a lasting memory in all who had the pleasure to meet him. ■

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