Wilhelm Simon (1929-1992)

There has traditionally been a curious gap in the training of the typical undergraduate in the UK. While everyone spends time learning quantum mechanics, pushing arrows in organic reaction mechanisms, and learning to count electrons to rationalise myriad inorganic structures, remarkably little time is spent on one of the key foundations of chemical science: measurement. Analytical chemistry, which underpins so much business activity, is often relegated to the margins. Is this an accident? Or is it an unintended consequence of the British class system? Just as in the old debates about “pure” versus “applied” science – analogous to the old “land” versus “trade” snobbery – analytical chemistry has often been seen as a kind of technical craft, useful for sure, but not really the deep intellectual quest that deserves a place alongside side “real” science. Yet, as these columns have argued, developments in apparatus and measurement invariably open doors to further investigation, and require skills that often cut across the traditional boundaries of the discipline. And before anyone starts to think that such snobbery is British phenomenon, the story of Wilhelm Simon, one of the key inventors of the potassium-selective electrode, shows that snobbery appears everywhere.

The story of its invention starts early in the 20th century with a piece of kit that transformed chemical thinking: Cremer’s bulbous glass electrode (CK 125, Feb 2018). The electrode’s ability to signal proton concentrations in real time was immediately exploited by Fritz Haber who used it to plot the changes in proton concentration during acid-base titrations. Coupled with Sørensen’s simple pH scale, Haber’s plots made acid-base equilibria much more conceptually accessible. Yet because the electrodes were tricky to construct and reliable measurement required extremely delicate quadrant or gold-leaf electrometers, electrical measurement of pH remained a niche area. Everything changed in 1934 when Arnold Beckmann and Henry Fracker were granted a patent for an “Apparatus for Measuring Acidity” which combined a much more robust electrode with a vacuum tube amplifier and galvanometer. Although based on very similar idea published in 1928, Beckmann had the business acumen to develop a device that was compact, rugged, and simple to use. Ironically, he offered the patent to the glassmaker Corning who decided that there wasn’t enough glass involved to make the device worth their while. Unfazed, Beckmann set up his own company; the new pH meters sold in their hundreds and then in their thousands becoming mainstays of both chemical and medical laboratories. Beckman became a big player and pH became a household word.

For other ions, however, measuring their concentration was far from simple. There was little choice but to take aliquots of the sample and to determine the ion content by using spectroscopic techniques like flame photometry – direct continuous monitoring was just a dream. Yet in the same year that Beckmann filed his patent, a tantalizing hint of future possibilities appeared in the literature. Two Hungarian chemists, Lengyel and Blum, reported that the composition of the glass was crucial in determining whether the electrode responded only to protons, or whether it was affected by other ions. They found that adding boron or aluminium oxides to the glass resulted in electrodes that showed significant sensitivity to sodium, an effect they attributed to ionic conduction through the structure. But the observation was not really useful because there was just too much cross-sensitivity to the presence of other ions.

Ten years later a biochemist working at the Harvard Medical School in Boston, George Eisenman, returned to the work. Interested primarily in the possibility of measuring sodium concentrations in living tissue, Eisenman enlisted colleagues at neighbouring MIT to make a series of glasses using different ratios of sodium, silicon to aluminium. Keeping the pH fixed he showed that one particular glass composition could be up to 250 times more sensitive to sodium than to potassium. This made measurement of sodium under real physiological conditions are real possibility. But Eisenman was not alone.

At ETH in Zurich, Switzerland, a young chemist, Wilhelm Simon, was thinking along similar lines. Born in the north of Switzerland he grew up in the bilingual region near Biel. He was an undergraduate at ETH and stayed on to get a doctorate in organic chemistry under Edgar

Heilbronner, famous for making some of the first deliberate investigations of chemical topology (he prepared the first Möbius hydrocarbon) at a time when the stereochemist Vladimir Prelog was Head of Department. But for all his specialisation in organic synthesis, Simon's interests lay elsewhere. He wanted to automate and simplify the more tedious aspects of chemical research. He developed and commercialized the first elemental analyser, a device capable of conducting Pregl's CHN analysis (CK99, November 2015) automatically and with much smaller samples. An automatic vapour phase osmometer followed, it too commercialised. Then he and his students developed a method to link gas chromatography with mass spectrometry, a development that would transform both the environmental and the biological sciences and open the doors to both medical forensics and "omics" in their myriad variants.

But it was his interest in automatic acid titrations that brought him to thinking about glass electrodes. After successfully constructing an automatic titration instrument, and frustrated by its cross-sensitivity to alkali metal ions at high pH, Simon and his student Dorothée Wegman made a systematic study of the behaviour of electrodes made from different commercially-available glass compositions. Their conclusion was that differences in electrical conductivity were critical in limiting the performance of the glass and that both the composition and the history of the electrodes influenced the extent to which the electrode was affected by sodium.

In parallel with this a group of commercially minded chemists set up a company in Cambridge, Mass., Orion Research Inc., to work alongside Corning – at last interested in electrodes – specifically to develop electrodes to sense more than just protons. After hiring Eisenman as a consultant, and innumerable abortive attempts to improve on his formulation, they too realised that a different approach was needed. It was while trying, unsuccessfully, to sense the concentration of calcium ions that James Ross, a chemist working for Corning with Orion, concluded that moving dications through glass just wasn't going to work – the binding to the silicate in the glass was just too strong. What, he wondered, if the binding sites themselves were mobile? In other words, if the glass in a pH electrode had originally been a model membrane, what if one went back to membranes for inspiration?

Membranes were well known to induce potentials. In 1911, Frederick Donnan at UCL had shown that when ionic solutions were separated by semi-permeable membranes, measurable electrical potentials appeared on either side of the barrier. Donnan's paper would rapidly become a cornerstone of electrophysiology and biochemistry, but it also inspired myriad experiments. In 1913, one of Haber's students Reinhold Beutner working with his graduate student J Loeb used an apple immersed in a salt solution as an electrode. Beutner and Loeb showed that while the choice of ions in the solution around the apple made no difference to the potential, their number and charge did, just as Donnan had predicted. They then made synthetic membranes out of oleic acid, guaiacol and cresol, and measured the potentials. The values were well below what Donnan predicted – the membranes were imperfect and the components were somewhat water soluble – but these synthetic membranes were reasonable models for the real thing. But given Loeb and Beutner's focus on biology, it never occurred to them to try to use their system in reverse, to measure a concentration.

Working fifty years later, Ross decided that rather than rely on glass to bind the ions, he would move the cation binding site from the glass into the body of the electrode itself. He sealed one end of a glass tube with a dialysis membrane and then filled the tube with a solution of a calcium phosphonate dissolved in a long-chain alcohol that was immiscible with water. With a silver/silver chloride wire providing the electrical connection, the difference in the calcium concentration between the inside and the outside of the glass gave a potential; the presence of the strongly calcium-binding phosphonate ligands in the solution ensured that sodium and potassium ions had almost no effect. The patent was a crucial milestone. But for various reasons Orion Research looked in other directions developing anionic sensors and building electrodes with solid salt rather than liquid membranes.

But binding sites for cations were a hot topic. In 1964 Berton Pressman at the University of Pennsylvania discovered the spectacular effect of the cyclic peptide antibiotics valinomycin, and nonactin which were able to completely disrupt ion pumping metabolism in mitochondria by increasing membrane permeability to potassium. Pressman showed that the effect was due to the ability of these peptides to discriminate between the alkali metals, binding to potassium rather than sodium or lithium. Ironically, Pressman's work was underpinned by the use of two or more different ion-sensitive electrodes simultaneously, each being used to correct the imperfections in another.

The idea of being able to bind an alkali metal was big news and both the chemists at Orion and Simon's group in Zürich immediately set to work to see whether these remarkably peptides could be made to work in an electrode. First Simon's graduate student Z. Stefanac established the stability constants for the potassium/peptide complexes using the group's vapour pressure osmometer. Then he tested set out to build a device. The electrode consisted of a glass tube into which was placed silver/silver chloride wire and a standard potassium chloride solution. At the end of the glass tube sat a fine glass frit soaked in a saturated solution of nonactin in carbon tetrachloride or benzene to act as the semipermeable membrane. Although relatively slow, the electrode was 750 times more sensitive to potassium than to sodium. Meanwhile in the US, the small team at Orion made similar observations, but could not match Simon's group for speed. To their chagrin, Simon would file the key patent (which gave due credit to Ross's membrane approach) forcing Orion to pay royalties for the use of the technology.

Simon's group were now the leaders in ion-selective electrodes, improving both their speed and their responsiveness; by the 1970's they had developed miniaturised microelectrodes that could probe the very heart of cellular physiology.

And yet, ironically, when Simon was promoted to the level of "ordinary" (full) Professor, it was of "Special Organic Chemistry", his university clearly still struggling to recognize analytical chemistry as a specialism in its own right. It was not until the 1980's that his lab was finally renamed the Analytical Chemistry Laboratory. Perhaps it is a reminder that the human mind is exquisitely tuned to sort and classify. But that teasing apart of the world leads to judgements, snobbery, and blind spots. Isn't it time we made it as normal to look across boundaries as it is to draw them?

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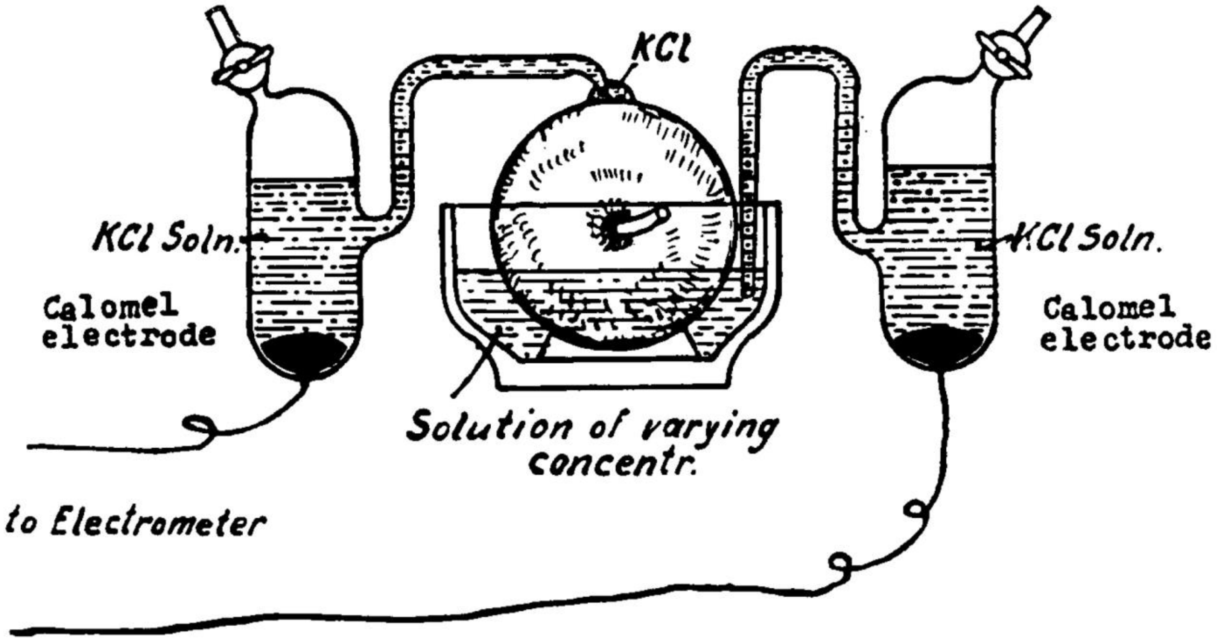
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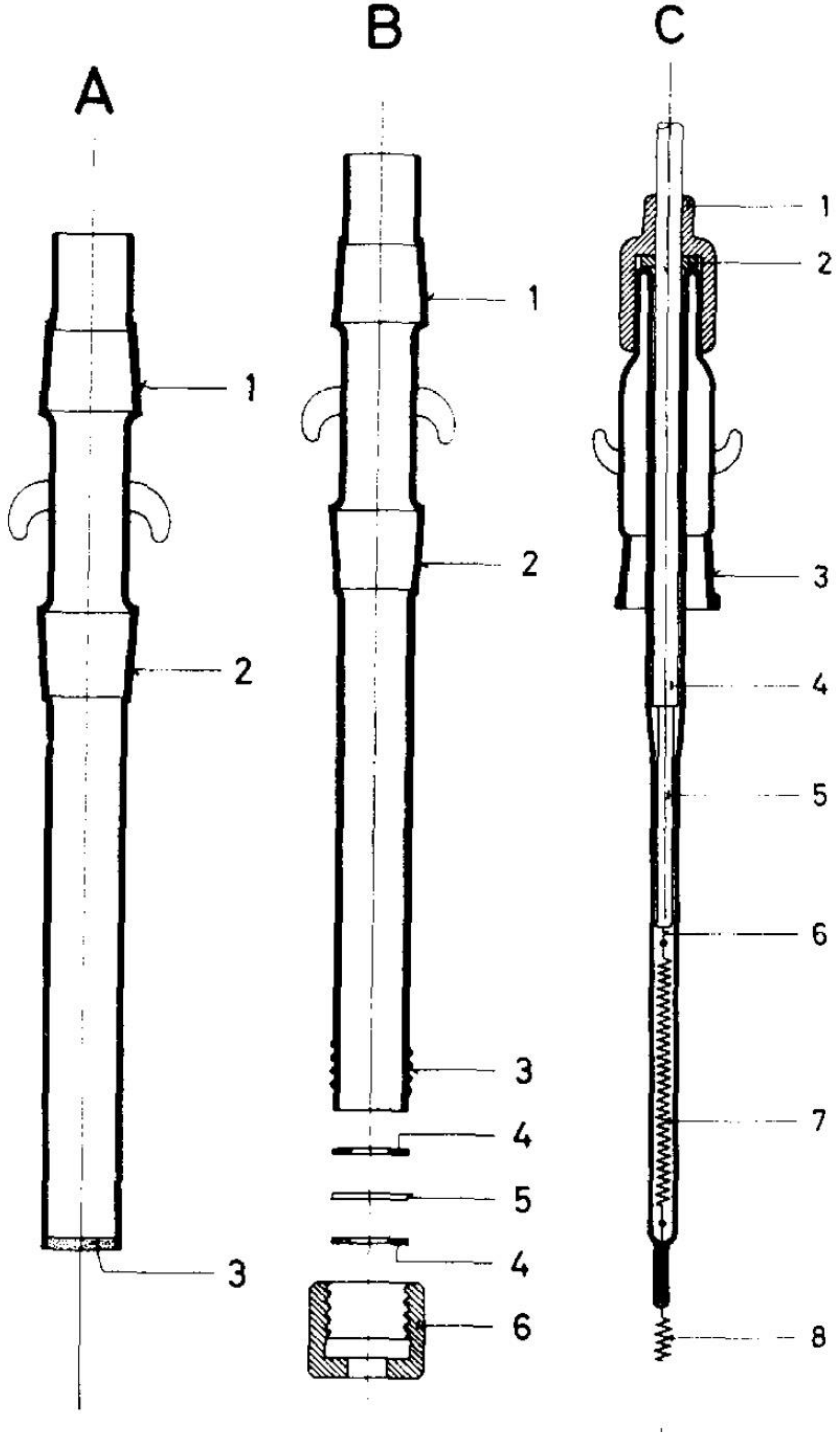
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