Sprinting before we stand

Mass spectrometry is an old technique. The history of the method goes back to the dying years of the 19th century and J. J. Thompson’s work on the electron. Old textbooks recount Aston’s work with the mass spectrograph. In the 1950s and 1960s mass spectrometry became a method of some importance in chemistry; affording a reliable means of determining the masses of molecules and information about atom connectivity by fragmentation of molecules, upon impact with energetic electron beams. For decades, mass spectrometry was the province of specialists, who spent much of their time in maintaining formidable pieces of equipment, perennially worrying about high vacuum systems. Since measurements required molecules to enter and ionize in the gas phase, the polar, high molecular mass substances, which abound in biology, were off limits to mass spectrometry. A few determined chemists toiled on derivatization methods to enhance the volatility of high molecular weight materials; a task which proved largely unrewarding. The first stirrings of a revolution were visible in the 1980s when new methods of ionization, electrospray techniques and matrix-assisted laser desorption, were introduced. Suddenly, mass spectrometry was ready to be pressed into the analysis of biological molecules; a flood of novel applications flowed in the decade of the 1990s, culminating in the award of a Nobel Prize to John Fenn and Keiichi Tanaka in 2002. Mass spectrometry quickly became the method of choice to analyse the ‘proteome’; a term commonly used to describe the total complement of proteins in an organism. The rapid advances in genome sequencing projects meant that translation of gene sequences would yield the sequences of ‘virtual proteomes’. Bioinformatics approaches might be expected to provide clues to the biological functions of proteins; although the task of ‘functional annotation’ has proved somewhat difficult. Since proteins are plentiful in body fluids and tissues, experimental analysis of protein profiles might be expected to be an indicator of biological status. Simply put, it might be possible to differentiate normal and disease states by analysis of subsets of the total proteome. Even more tantalizing is the prospect of developing protein markers, which might signal the early onset of disease; permitting clinical intervention well before physical symptoms are manifest. Inevitably, mass spectrometric analysis of body fluids is being advanced as the method of choice for proteomic analysis. This superficial primer on mass spectrometry and the proteome would be out of place in these columns if it had not been for a news feature entitled ‘Running before we can walk’, that appeared recently in Nature (2004, 429, 496).

The Nature report highlights a proteomic test for cancer, described in a 2002 paper entitled ‘Use of proteomic patterns in serum to identify ovarian cancer’ (Petricoin, E. F. et al., Lancet, 2002, 359, 572). This paper appears to have prompted a US Congressional resolution ‘urging continued funding to drive a new diagnostic test towards the clinic’. Good diagnostic tests must overwhelmingly identify samples from patients known to suffer from disease and have an acceptably low level of ‘false positives’, in control samples. The test reported by E. F. Petricoin, and L. A. Liotta, the lead authors of the Lancet paper, seemed to fulfil these criteria; the first steps to commercialize followed. Unfortunately, independent analyses quickly cast doubt on the claims of the Lancet paper, suggesting that the differences in serum mass spectral profiles of cancer patients and normal controls were artifacts and not a result of genuine differences of biochemistry. The critics used raw data available on an Internet site. Curiosity drove me to the original Lancet paper and the mass spectral data on the NIH/FDA Clinical Proteomics Program Databank (http://clinicalproteomics.stern.com). Reasonably familiar with conventional mass spectrometry, I was bemused to find digitized spectra, with intensity data reported at unreliable low mass values; a range where the major differences lay between normal and control samples. The language of the spectroscopist had been discarded for the sleight of hand of the statistician. My naive conception of the proteome was conspicuously missing in the ‘proteomic patterns’ of the Lancet paper. Mass spectrometry of a complex biological mixture was reduced to a ‘fingerprint’; clinical diagnostics suddenly seemed to be a sophisticated pattern matching game, with proteins, genes and biological chemistry receding into the background. The Nature report’s title
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‘Running before we can walk’ seemed conservative; ‘Sprinting before we can stand’ seemed more appropriate. The waters were further muddied when the principal authors of the Lancet paper were implicated in a controversy involving inappropriate consulting practices, in a US Congressional hearing.

By itself, the cancer proteomics diagnostic controversy would be only another one of the many contentious scientific debates, that occur with great frequency, in high profile areas of biomedical research. The affair, however, raises a more general issue; the growing tendency to rush headlong into the application of sophisticated instrumental methods to clinical and biological problems, with complete disregard for the technical issues involved. Modern biology is driven by extremely sophisticated equipment and expensive reagents, making competitive research a very costly business. NMR spectrometers, mass spectrometers, DNA microarray scanners, DNA sequencers, confocal microscopes, X-ray diffraction equipment, cell sorters and an assortment of separation and analytical equipment are common currency in modern biological research. Superconducting magnets, lasers, high vacuum systems and optical devices which were once found only in physics departments are now integrated into user-friendly, commercially available instruments.

The advertisement pages of many journals are a testimony to the technical sophistication that has come to be commonplace in biology research today.

In the last few years the pace of acquisition of major instruments in university science departments and national laboratories in India has increased substantially. This is a result of enhanced budgetary support, with the FIST program of DST providing a special thrust in the academic institutions. Equipment ranging in cost from $100,000 (Rs 45 lakhs) up to, and sometimes beyond, $1 million (Rs 4.5 crores) have been purchased. But in most centres installation has been slow, with local infrastructure like power, air-conditioned rooms and sometimes, even water being rate-limiting. Progress after installation has also been slow, with the lack of trained technical staff to man facilities, being the most frequently cited excuse. The absence of a cadre of trained, well-paid technical staff is a characteristic of Indian academic institutions. The contribution made by the new facilities to uplifting the quality of ongoing research programs has been limited by the inadequate appreciation of the necessity to learn techniques well, before applying them. The absence of a culture of academic collaboration and the technical innocence of many who are keen to apply the latest tools to their pet problems, further hampers rapid progress. In many places the ‘engineers’ of the companies that sell equipment are the major advisors to facilities; a situation similar to that in the medical profession, where representatives (invariably unqualified) advise doctors on the virtues of the most recently introduced drugs. But the most disconcerting problem is the tendency of many researchers, students and senior scientists among them, to assume that expensive and sophisticated equipment are the key to solving scientific problems. The need to acquire a minimal degree of technical competence is never emphasized; the ability to look critically at data generated by instruments is rarely stressed, even to beginning research students in India. Many researchers approach major facilities, following an old principle enunciated in his Nobel lecture by one of the founders of chromatography, A. J. P. Martin: ‘Nothing is too much trouble if somebody else does it’.

The growing body of uncritical, technically inept professionals is a matter of some concern. In the area of biomedical research (and in other high profile areas like nanotechnology) there is a tendency to claim great success at the slightest provocation. How many diagnostics and vaccines have been launched in the newspapers and at ministerial functions? With the latest tools of modern biology becoming available and with genomics and proteomics becoming commonplace, there will be many claims of dramatic success in these fields in the near future. How can these be assessed in an environment, where the critical faculties are often suspended? The cancer proteomics story with which I began this column is a pointer to the urgent need to promote critical and competent analysis to assess the claims of new technologies; the ability to distinguish fact from artifact must be prized. Even more importantly, it may be essential to enhance the technical training imparted to new students in PhD programs, so that they are able to cope with the increasing sophistication of instruments in many tumultuously advancing fields. We must learn to stand before we sprint.

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