Decentralised Testing Technology – Past, present and future

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The history of decentralised testing or point-of-care testing (POCT) technology is essentially a history of sensor technology. If one broadly defines a sensor as a device that transforms chemical information directly via a transducer into a measurable signal, then one of the first sensing technologies to be used outside of the laboratory were electrochemical sensors for whole blood pH and blood gases. These were incorporated into the first commercial, blood gas instruments in the 1950s and while they were mainly used in laboratories, some were placed closer to the patients, within Intensive Care Units. Since then, there has been considerable progress in the development of chemical sensors and the introduction of a whole new generation of technologies in the form of biosensors.

Biosensors are sensors which incorporate a biological or biologically-derived sensing element and there would probably be few other diagnostic technologies which have received as much attention and predictions about their future market impact. While many of many of the predictions have not materialised, the number of devices becoming commercially available is increasing.

Estimates vary greatly, and are dependent upon the country, but it is believed that in 2001, approximately 25% of the total chemistry market is performed using sensing related technologies. This market is dominated by one extremely successful biosensor technology, namely whole blood glucose sensors which now allow diabetics all over the world to monitor their blood glucose within their own home, as well as glucose testing within hospitals and clinics.

The first glucose sensor was for urinary glucose and appeared about the same time as the first commercial blood gas instruments in the early 1950s. But the real breakthrough came in 1962 when the inventor of the oxygen electrode, already used in many blood gas instruments, described how this electrochemical sensor could be made more intelligent by adding enzyme transducers as membrane enclosed sandwiches. The Clark-Lyons enzyme electrode was born and with further modifications, appeared as a commercial analyser in 1973, the Yellow Springs glucose analyser using amperometric detection of hydrogen peroxide.

At about the same time, Boehringher Mannheim introduced their first glucose meter, a device which measured the colour in a test strip impregnated with glucose oxidase/peroxidase, following reaction with the glucose in a drop of capillary blood. This reflectance technology is still used in many parts of the world but is gradually being replaced by electrochemical transducers. The technology used to make the glucose strips, so-called thick-film sensor technology, has evolved considerably in the past 20 years, the consequences of which include ease of use for the operator and significant reductions in the time between applying the blood to the strip and obtaining a result. Another consequence of the development of thick-film technology has been the ability to make reusable sensors as opposed to the single-use sensors incorporated in glucose strips. To make an enzyme sensor respond repeatedly to multiple blood samples, over a period of several weeks, has been a considerable challenge and this was one of the reasons for the long period of time which elapsed between the initial development of thick-film, reusable sensors and their commercial appearance. Added to this difficulty were those of incorporating such a sensor in the complex fluidics of a blood gas analyser and ensuring that the sensor was not subject to major interferences.

These challenges have now been overcome and metabolite sensors for parameters such as glucose, lactate, urea and creatinine can be incorporated into what are now called critical care analysers as opposed to just blood gas analysers. Thus, apart from glucose strips, the most common point-of-care tests are those carried out on bench-top analysers such as the Roche OMNI, which measures pH, gases, electrolytes, metabolites and haemoglobin derivatives or co-oximetry.

As an alternative to relatively large, bench-top analysers, the last decade has seen the appearance of smaller, hand-held devices for both measurement of single and multiple parameters. The application of so-called thin-film manufacturing technology to sensor production has been instrumental in the development of small sensor arrays. The technology is similar to that used

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to manufacture silicon chips with each constituent layer of the chip or sensor being microfabricated using masking and etching techniques which are well established in the computer industry. The results are small single-use cartridges containing an array of electrochemical sensors which operate in conjunction with a hand-held analyser, the whole concept being introduced in the 1990s as the I-Stat analyser.

The small size of such devices certainly facilitates their use at the bedside, the ultimate in point-of-care, and many companies are currently investing in microfabricated or miniaturised devices for molecular detection of infectious agents and other disease markers which can be used at point-of-care. As yet, few of these devices are available but the sequencing of the human genome will undoubtedly drive the commercial development of so-called gene-chips.

Apart from significant advances in sensor design for glucose and the traditional critical care parameters, the last 5 years have seen the long-awaited commercialisation of immunosensors. Thus, it is now possible to measure many different proteins and hormones on whole blood but most interest has centred on cardiac markers and many small devices and analysers such as the Roche Cardiac Reader and Cardia Status from Spectral, are now available which can measure troponins, CK-MB and myoglobin. Advances in surface chemistry such as lateral flow techniques for separation of the bound protein or hormone have made a significant contribution to the success of these devices. Other important components include the use of biotinylated antibodies and gold sol particles with detection of the final signal usually by optical techniques.

Coagulation testing in the laboratory has increased enormously in the last decade, partly through clinical advances and partly through automated technology. In recent years measurement of parameters such as Prothrombin Time and Activated Partial Thromboplastin Time can also be measured in the ward or in the patient's home through a variety of devices. In fact, the benefits of point-of-care coagulation testing are better documented than for many other parameters and this will clearly drive the continuing development of small coagulation devices. The main principles behind small coagulation devices are detection of optical motion using either magnets or by laser light interference. It is likely that other and more specific coagulation parameters will be detected by immunosensors in the near future.

The above represents a brief and selective overview of sensor development over the last 50 years and these technological advances have clearly been one factor in the development of decentralised or point-of-care testing. Advances will continue and these will be directed towards measuring new parameters and, perhaps more importantly, they will address the limitations of the technologies discussed above.

Five years ago, most laboratory professionals would probably have highlighted quality as their major concern about point-of-care testing. Such concerns related both to the precision of POCT devices and to their accuracy, particularly when comparing results to those obtained for the same parameter in the central laboratory. However a recent review from the US indicated that concerns about quality have diminished which is a testament to the effort made by manufacturers on this particular issue. Improvements in the quality of glucose strip technology over the last five years are well documented and this has been achieved in a variety of ways. One example is the change made by at least one manufacturer to an enzyme measurement system which is not susceptible to oxygen interference, a major cause of poor accuracy with glucose strip methods.

One of the growth areas for POCT is predicted to be the home testing sector and this raises a current concern for many laboratory professionals which is the possibility for errors when devices are used by non-laboratory personnel, particularly patients within their own homes. The area of ease-of-use of devices has not been neglected by manufacturers. To take glucose strip technology again as an example, most manufacturers have introduced non-wipe strips thus removing a major source of operator error for this measurement. Yet, the goal for many laboratory staff who have to supervise the use of POCT devices is a fool-proof instrument. This is a difficult if not impossible target for manufacturers and currently the area of instrument design is probably a tougher challenge than that of perfecting the measurement process.

However efforts will no doubt continue to simplify instruments but it has to be realised by customers and users that there is a significant cost associated with making devices user-friendly. Already, POCT technologies are priced at such a level which precludes them for use in many parts of the world and even in those countries with highly developed health care systems, laboratory professional often draw unfavourable comparisons between the cost of POCT testing and testing done in the central laboratory. The lack of studies which show that the cost of testing can be offset against the benefits of improved patient outcomes is a major limitation at the present time. Hopefully, attention will focus on this area now that other concerns such as quality have largely been addressed.

Finally, the last but probably the most important area of concern by POCT users at the present time, is nothing to do with what has been the main topic of this presentation so far, namely sensor technologies. Instead it is about the application of information technology and what happens to the patient and quality assurance data after the measurement process. The linking of POCT instruments to laboratory information systems (LIS) has been termed "Connectivity" and the difficulties of doing this, or "Lack of Connectivity" was highlighted by a survey conducted on behalf of the American Association of Clinical Chemistry in 1999. It showed that although POCT is widely practiced in the US, only 16% of POCT instruments in US hospitals are electronically

connected to the laboratory information system. Similar comments on the need for easier interfacing of POCT devices to information systems have been made in many other countries.

The need for a link to the LIS or other information system is crucial because without it patient data may be lost. In addition there is no possibility to add value to the data via tools such as decision support systems and perhaps most importantly, it will seriously undermine the implementation of the electronic patient record.

In response to the demand by users for an easy way to integrate or connect POCT instruments into the laboratory or hospital information management systems the AACC requested Agilent Technologies to organise an open meeting of POCT manufacturers, LIS/HIS suppliers, health care providers and consultants. This took place in October 1999 and the result was the formation of the Connectivity Industry Consortium or CIC.

The CIC is an open, not-for-profit, industry-based organisation, currently composed of 36 members from device manufacturers, information system vendors and health care providers. During the last 12-15 months the CIC has produced a standards-based connectivity solution for POCT devices and is about to donate the standard for further maintenance and refinement to an existing, established industry standards-setting organisation selected by the Consortium. This will be in a manner similar to standards such as HL7 or ASTM.

For the user or laboratory scientist it will mean that all POCT products produced by manufacturers who are members of the CIC, will incorporate the same bi-directional connectivity standard. This will greatly facilitate the linking of devices to the information technology systems in their institutions and it will address one of the major, current limitations of POCT technology.