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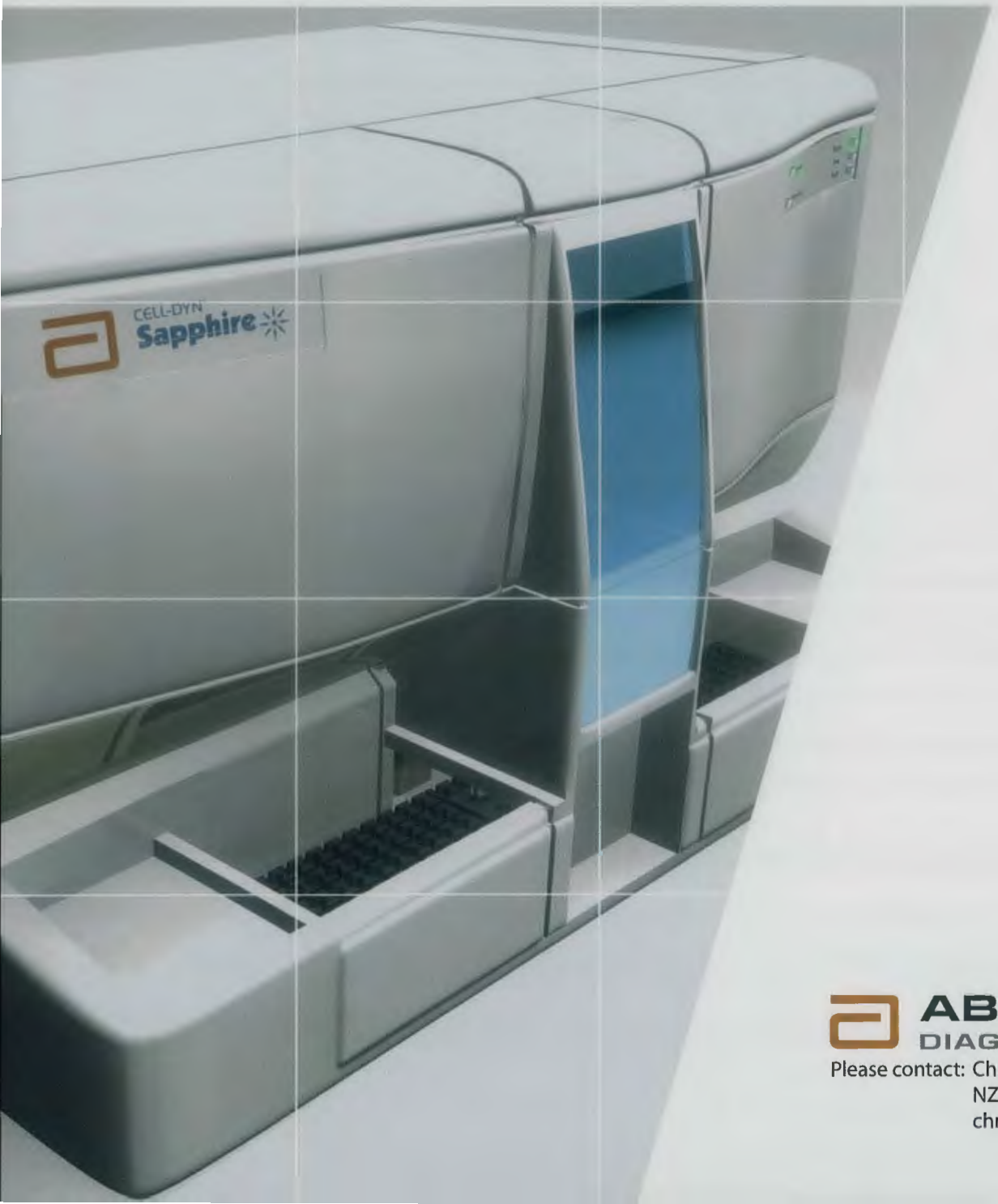

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Review of point of care testing (POCT) and the evaluation of whole blood for potassium and glucose on the Roche Reflotron®.

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Abstract

Point of Care Testing (POCT) or Near Patient Testing (NPT) is perceived to benefit the patient with faster turnaround times (TAT) and with the potential for improved, more responsive clinical management. But the financial costs of point of care testing along with other potential disadvantages need to be considered before implementing a POCT program. In some communities, especially where the nearest laboratory may be several hours away, some POCT may be considered necessary, although currently only a small proportion of the laboratory repertoire can be considered suitable for POCT testing. Some major factors to be considered before offering POCT include cost per reportable test, staff training and ongoing competency, service and instrument maintenance, quality control, data management and who is ultimately responsible for the test result, to name just a few.

Southern Community Laboratories currently have available Roche Reflotron® instruments for satellite centres. A Medical Centre has been supplied with an analyser. We currently use serum as the specimen of choice on the Reflotron®, but this imposes a 30 min pre analytical time to allow for clotting and centrifugation of the sample. A preliminary study was conducted to determine the feasibility of further investigating the use of whole blood for POCT in a General Practice (GP) surgery. The use of a whole blood sample removes the requirement for centrifugation of the specimen and allows a faster turn around time.

Twenty apparently healthy volunteers donated 20mls blood for comparison of whole blood and serum sample types. Glucose and potassium analysis was carried out on a Roche Reflotron(. The mean difference between serum and lithium heparin whole blood was 0.137 mmol/l for glucose (95% confidence interval: -0.022 to 0.296 mmol/l over the analytical range of 4 to 8 mmol/l, p = 0.0867). The mean difference between serum and lithium heparin whole blood for potassium was -0.275 mmol/l (95% confidence interval: -0.365 to -0.185 mmol/l over the analytical range of 3.4 to 4.8 mmol/l, p = <0.0001). Assessment of potassium intra-assay imprecision for whole blood gave a mean of 3.57 mmol/L with value for coefficient of variation (CV) of 1.1%, for plasma the mean was 3.57 mmol/L with a CV of 1.3% and for serum a mean of 3.84 mmol/L and CV of 0.8%. Assessment of glucose intra-assay imprecision for whole blood gave a mean of 5.43 mmol/L with CV of 1.6%, for plasma a mean of 5.76 mmol/L with a CV of 1.9%, and for serum a mean of 5.22 mmol/L and CV of 2.7%. Assessment of potassium inter-assay precision for plasma gave a mean of 3.68 mmol/L and CV of 1.7%, for serum a mean of 3.80 mmol/L with a CV of 1.7%, and for Roche Precinorm quality control a mean of 3.61 mmol/L with a CV of 2.3%. Assessment of glucose inter-assay precision for plasma gave a mean of 5.85 mmol/L with a CV of 2.4%, for serum a mean of 5.36 mmol/L with a CV of 1.9%, and for Roche Precinorm quality control a mean of 6.41 mmol/L with a CV of 2.5%.

Although this study was very limited, inter- and intra- assay imprecision for each sample type for both analytes was acceptable according to our laboratory protocol (acceptance value of CV less than 5%). The difference between serum and lithium heparin whole blood was not statistically significant for glucose for the range of values observed. However, a wider range of values is required to confirm this. The difference between serum and lithium heparin whole blood potassium was significant. The significantly different mean potassium obtained with whole blood indicates this may not be a suitable sample type for potassium analysis on the Reflotron®.

This study was designed as a preliminary investigation into POCT implementation and on the possible use of whole blood for POCT in a community medical centre. As a result, only a limited range of testing and result values were obtained. Further studies are required to fully evaluate the use of whole blood specimens as a sample type to be used on the Reflotron" before this is considered to be appropriate for use by this laboratory. Implementation of a POCT site requires careful consideration; planning and on-going support to ensure an efficient and effective operation is in place. Quality assurance is a critical aspect of POCT testing that is often overlooked by non-technical personnel.

Keywords: point of care testing, near patient testing, whole blood, potassium, glucose

Introduction

In the last 2 decades, there has been a rapid increase in the availability and usage of Point of Care Testing (POCT) in the hospital, community and home environments. Before implementation of a POCT facility, careful consideration must be made by all parties of the potential benefits and disadvantages of introducing such testing.

In the general practice environment, potassium is a useful measurement for the routine monitoring of patients in chronic renal failure or in patients on certain medications. Glucose is routinely measured to monitor patients with diabetes mellitus. The object of this dissertation is to review POCT in general with a secondary objective to investigate the feasibility of using whole blood as opposed to serum for a sample type on a Roche Reflotron" analyser and thereby eliminating the requirement for sample centrifugation.

Review of Point of Care Testing in general

A definition for POCT is testing at or near the site of patient care. The main objectives are to improve medical and economic outcomes. The faster the patient is restored to health, the less cost to the health care system. In today's society, people are taking more responsibility for their own health and well-being. They expect to receive the best medical care, which includes fast and accurate diagnosis of their ailments. Turn around time (TAT) of laboratory results are expected within days or sooner rather than weeks, as may have been the case previously in the community. In the hospital setting, results may be required within minutes to allow for appropriate treatment in a medical emergency.

In the hospital environment, POCT can be found in the wards, emergency and critical care units. The claimed benefits of POCT include more rapid turn around time (TAT) of results. This can result in a rapid diagnosis or recognition of a life threatening condition and supports the ability of physicians to apply decision criteria to launch

rules for further optimization of treatment and monitoring of patients. POCT can also help to prevent a crisis, alter therapy; accelerate hospital admission or discharge, decrease the need for ancillary services, blood transfusions, inappropriate drug therapy, number and frequency of critical care admissions, and decrease length of stay (1).

In the community environment, POCT can be found in the surgery, pharmacy or in the home. It is generally not regulated and not supported by the community-based laboratory. Rapid results at the time of the consultation may decrease the need for a further visit, enable alteration of treatment or determine the need to send a patient to hospital.

Careful consideration is required though before offering POCT. What is the environment / location for the testing? Does POCT provide any information that can be acted upon at the time of the results? If not, what is the purpose of doing the test? Where and when is the test done? What level of imprecision is needed or acceptable? What are the costs? Hospital and community services differ in their requirements and these factors along with the perceived economic and medical benefits will vary depending on who the stakeholder is and what the likely perceived benefits is.

Financial evaluation of POCT services is difficult. The cost of POCT can be prohibitive, especially if the volume of testing doesn't justify the cost of the training and regulatory compliance required for non-laboratory personnel. Jacobs found that, even though the average cost for POCT glucose for a particular hospital was $7.11 (US), the range for the various sites was $5.71 - $132.22 depending on the number of tests performed (2). Inappropriate testing ('because its there') also adds to the cost of testing. Tests designed for POCT can contain numerous built in checks and balances for error free, easy operation, but often come at a price. Implementation of POCT may be more expensive and direct costs higher, but it is possible that savings may occur in the long term. Faster test results could reduce the total cost of the health episode or help to lower hospital admissions, generate fewer emergency room visits, and ensure use of correct treatment plans. These gains may offset the cost of POCT. Conversely, delay in results from the laboratory however, may mean inappropriate or delayed treatment, another visit to the GP, inappropriate hospital admission, possible further (inappropriate) testing, and increased cost. As manufacturing processes for POCT devices develop, prices for reagents and disposables should drop, thus making POCT more economically competitive to alternative testing regimes. Having assessed the direct and indirect costs of POCT, how do you apply a financial cost figure to patient and clinician satisfaction? This also comes into the equation.

Hypothetically, significant financial savings could be made though, depending on the circumstances in which the POCT is utilised. Collinson reported significant cost savings when cardiac markers were introduced as a POCT for patients presenting with chest pain to an emergency department (1). In this study, biochemical confirmation of acute myocardial infarction (AMI) was required in 90% of patients presenting to a routine hospital emergency department (ED) with suspected acute coronary syndromes. In a randomised controlled trial of POCT in the ED and critical care unit (CCU), the median TAT dropped from 72 minutes (central laboratory testing) to 20 minutes using POCT for cardiac markers. In patients considered low risk, there was also a reduction in the length of hospital stay (209 minutes using laboratory testing vs.150 minutes using POCT). When the results of this study were applied to a cost model previously developed by the author, a potential saving of 0.5 million pounds was feasible. They concluded that rapid diagnosis is cost effective, but only within the context of data driven decision-making protocols.

Brogan (3) reviewed the use of POCT to rule out AMI on a coronary care unit (CCU). The availability of CKMB and myoglobin for re-triage of non-AMI CCU patients suggested potential savings of more than $200 million (US) per year nationally.

POCT testing by the general practitioner should be scrutinised using the same criteria as within a hospital environment. In Denmark, general practitioners mail blood tests for C-reactive protein (CRP) to the hospital for analysis. A randomised crossover trial designed to assess the clinical, organisational and economic consequences of implementing POCT for CRP at the general practitioner surgeries was undertaken by Dahler-Eriksen and colleagues (4). Although the trial showed cost savings for the hospital laboratory by measuring the CRP in the surgery, there was no significant change in antibiotic prescription. According to the authors, if there was follow-up after POCT implementation by clinical education and guidelines, the cost savings could be further increased by a reduction in erythrocyte sedimentation rate (ESR) testing and more appropriate use of antibiotics.

Benefits for the patient should also be considered but to what extent do we do this? For example, prostatic specific antigen (PSA) testing from a whole blood sample that is available at initial consultation in the physician's office could be convenient for both the doctor and the patient. Further follow-up can be arranged straight away depending on the result. Piironen and colleagues performed a study to validate the use of a whole blood sample for the determination of circulating forms of PSA (5). They concluded that PSA performed within the time frame of the physicians office visit on whole blood would provide results equivalent to conventional analysis using serum. But should we be measuring PSA using POC technology? Does convenience outway cost? Is a PSA produced in 5 minutes on a device with questionable quality better than waiting 24hrs for a laboratory produced result that supposedly is more reliable? Follow-up can be arranged by letter or phone and not necessarily requiring a further consultation. A delay between testing and review allows consideration of further primary options by the doctor and patient. These are just some of the questions that we should be considering. Having the technology available doesn't necessarily mean that we should be utilising it regardless.

Ideally, POCT testing should only be used where results will immediately influence the patient outcome. In diabetic patients, blood glucose levels can change rapidly in 15 minutes depending on food intake, stress, and dose of hypoglycaemic agent taken (6). Thus rapid turnaround times are required in some cases so that appropriate intervention can be taken. People with diabetes mellitus can monitor their glucose levels at home. Studies have shown that more frequent home monitoring and careful management of treatment can lead to fewer complications, and patients are more likely to be in good control when self monitoring (7, 8).

In 1993, The Diabetes Control and Complications Trial Research Group (DCCT) conducted a multi-centre, randomised clinical trial designed to compare intensive treatment with conventional therapy with regard to their effects on the development and progression of vascular and neurological complications of insulin dependent diabetes (type 1). The study population was 1441 patients followed for a period of 6.5 yrs (range 3 - 9 yrs). The results showed a 76% reduction in retinopathy, a 54% reduction in nephropathy, and a 60 % reduction in neuropathy in the intensive treatment group (7).

In the United Kingdom in 1998, the UK Prospective Diabetes Study (UKPDS) Group conducted a randomised controlled trial studying the effects of intensive treatment on patients with non-insulin dependent diabetes (type 2). Newly diagnosed patients (3,867) were randomly assigned to intensive treatment involving the use of sulphonylurea and/or insulin, or the conventional group where treatment was diet alone.

As in the DCCT, a reduction in diabetic complications was observed in the intensive treatment group (8).

Aubert and colleagues conducted a randomised controlled trial to review the effect of the use of nurse case managers and intensive therapy on improvement on glycaemic control in diabetic patients (9). The study involved 121 Type 2 patients and 17 Type 1 patients. Seventy-two % of the patients completed follow-up. Of these, the intensive therapy group had an average drop in HbA1c of 1.7% compared with 0.6% for the conventional treated group, and a mean drop in fasting blood glucose of 2.38mmol/L compared with 0.83mmol/L for the conventional treated group. Thus, the availability of POCT devices is important for the self-management for diabetic patients in order to monitor and adjust their treatment. Being able to manage their diabetes will enable them to lead a more fulfilling life. Similarly, the availability of prothrombin meters will enable patients receiving warfarin to manage their life.

However, the effect of POCT in decreasing TAT does not necessarily affect the overall outcome of the health episode. Kendall and Reeves showed that in a randomised controlled trial in their accident and emergency department, only 7% of patients having POCT testing had their management altered as a result of the POCT testing (10). Testing did not alter the amount of time that was spent in the department, length of stay in hospital, admission rate, or mortality, suggesting that laboratory results were not the limiting factor, and improvement in reduced TAT did not seem to improve clinical outcome of the patients.

Other investigators have also come to the same conclusion. Nichols and colleagues investigated test results availability and the effect on waiting times for cardiovascular procedures (11). They concluded that decreasing TAT does not necessarily improve the patient outcome and that POCT results will not offer improved TAT in critical care situations if the physician requires more than the POCT result to make a clinical decision. Often systematic changes in workflow around POCT are required to achieve the greatest improvement of patient waiting time. Delay in clinical acknowledgement of results often contributes to the delay in patient management. Thus, the question must be raised, why have the POC testing available if the results are not going to be acted upon?

A more recent evaluation on the impact of TAT and length of stay (LOS) in an emergency department was conducted by Lee-Lewandrowski and colleagues (12). They evaluated TAT, LOS, and physician satisfaction in the emergency department of the Massachusetts General Hospital, Boston before, and after implementation of POCT in the form of a 'stat laboratory' in the emergency department. The test menu was limited to glucose, urine dipstick, pregnancy testing, and cardiac markers. Designated technical staff members were appointed to the POCT laboratory, thus enabling regulatory compliance without the need to train and maintain competency of many emergency department staff. The pilot study had a positive impact on TAT and physician satisfaction. Operational improvements were implemented after the study was conducted. It would be interesting to find out if the positive effects on TAT and LOS in the ED continued after the conclusion of the study and what the impact was on the overall health episode. That is, what effect does this have on mortality, morbidity, length of stay in the hospital, and potential cost savings outside the confines of the study period.

Introduction of POCT to some environments may have significant impact on the operators. For example, nurses may have little free time for QC, documentation and training. These issues also need to be considered. Co-operation between the laboratory and the POCT site can help minimise the impact. There is also the effect on the laboratory to consider, including support costs, labour, documentation, cost of initial training, ongoing competency, and the potential loss of tests from the laboratory and thus loss of revenue. Training requires significant resources, especially if there is a large number of operators or significant staff turnover. It is common that a non-laboratory staff member does the POCT testing. Thus, initial and ongoing training is vital to ensure a laboratory 'culture' is in place, i.e. QC samples are assayed, reported and acted on, positive patient identification occurs, documentation is kept up to date, results recorded, and so on. Manufacturers often provide this initial training, but a program needs to include ongoing training and competency checks. It is advisable that this is done in conjunction with the laboratory. The laboratory will have a significant role in the development of POCT programmes and their expertise should be utilised to make the introduction and ongoing upkeep a success for all parties concerned.

Quality assurance

Quality and quality management should be just as relevant to the POCT site as it is to the central laboratory. However, quality has a different perspective depending on the stakeholder. Laboratorians have an objective view of quality that is measurable, for example calibration, quality control, accuracy and precision. Clinicians, nursing staff and financial managers tend to have a subjective view on quality - patient outcome, convenience and financial cost. Because of the increasing popularity of POCT, it is increasingly important that quality standards are in place and maintained in the POCT environment.

Quality assurance (QA) is an overview and examination of a complete process, from approaching the patient with the intention of obtaining a sample, to looking at the subsequent result report from the laboratory or POCT analyser. Problems associated with POCT include lack of QC testing, and failure to act when QC indicates poor performance, as well as poor maintenance, poor result recording, poor documentation, failure to recognise false results, interferences, and failure to follow procedures, (including standard precautions and safe work practices). Staff working in non-laboratory environments may fail to recognise these potential errors.

The quality of POCT must remain high, otherwise the advantage of quick TAT and convenience are negated by inaccurate results creating more problems for the patient or clinician. Non-laboratory staff rather than lab-trained professionals must respond to results generated quickly. However, they are often unfamiliar with quality practices associated with testing and the testing process is not as tightly controlled as the laboratory. In some cases there is no quality assessment / assurance or even control of the process. If quality control is not conducted or reviewed when required, how can we be confident that the analyser or reagents are functioning properly, or that the operator technique is correct, or even that the results are reliable?

A POC analyser that has the capability to perform QC automatically is likely to be more useful than one that relies on operator intervention for QC, although this feature may add to the cost of the analyser. These analysers automatically draw samples from an onboard supply at an operator (or laboratory) defined schedule, thus ensuring that the QC is performed routinely. This form of QC checks the analytical process but does not check operator technique and thus should be considered supplementary, but it does ensure that the analyser is at least functioning properly.

It is important that QC practices suit their purpose. Glucose meters used in the hospital / clinics have many operators using the same device on multiple patients. Here sampling technique varies with the operator and thus QC is important to check both the operator technique and the analytical performance of the device. Devices used for self-monitoring of treatment by the single user in the home environment generally do not have QC performed regularly. These devices are generally used for treatment monitoring and consistency is

considered more important than accuracy. As only one person is using the device, adequate performance is assumed due to the consistency of the sampling technique. QC is still required to verify performance of the device and this can usually be done by the user or at pharmacy / clinics on "check" days. For glucose meters the American Diabetes Association (ADA) recommends that these devices have a total error of 10%. Newer devices have a goal of 5%. A study done by Weitgasser and colleagues in 1999 on the new generation meters showed that these were more accurate when compared to the older devices, but that the performance still did not met the ADA recommendations in the hands of an experienced operator (13). Only 49-56% of the values measured on the new devices met the ADA criteria of target total error of <5%.

Quality of results can also be affected by a number of variables in the POCT environment as it can in the laboratory situation. These can be classified into pre-analytical, analytical, and post analytical. Pre-analytical variables include such issues as positive patient identification, appropriateness of the test request, patient preparation, taking the appropriate specimen at the appropriate time, medications, reagent storage, temperature, and environmental conditions (14,15). Sample collection is a vital part of the QA process. Common sources of error include incorrect patient identification and poor sample technique. Shallow skin puncture in capillary collections leading to slow blood flow, squeezing too hard, scooping the blood along the skin as it dribbles from the puncture site, milking the heal or digit, and puncturing in an awkward or incorrect spot all add to potentially incorrect results. Analytical variables include technical issues, e.g. calibration, control, sample haemolysis, analyser operation, and operator technique. Post analytical variables include transcription of results, and interpretation. The operator needs to be aware of all these issues along with other variables that influence the quality of the result. For example, as blood substitutes come into use, their effects on point-of-care testing needs to be evaluated (16, 17).

Le Grice's article (18) states that *"reports of blood glucose monitoring in the non laboratory based setting found that unacceptable errors are 3 times more likely to occur than with laboratory based assays despite the excellent optical precision of these glucometers."* Reasons identified were:

- Unsatisfactory sample collection
- Improper calibration
- Improper application of the sample to the reagent strip
- Accumulation of the cotton fibres in the optical compartment after wiping
- Incorrect location of the strip in the meter
- Contamination of the optical compartment
- Defective or outdated strips

Errors can generally be categorised into three major areas of responsibility: technology, device operation, and test performance (19).

What are the criteria for POCT?

In the hospital environment, POCT committees are commonly set up, where members are from all areas of the healthcare system including Information Technology and regulatory services, and careful evaluation of the purpose of setting up a POCT is undertaken. Such a committee needs to evaluate POCT and address all the issues previously described. They need to develop policies, procedures and systems, ensure training and ongoing competency occurs, and address regulatory requirements. Generally, a POCT coordinator is appointed to coordinate documentation, training, maintenance, calibration, quality control (QC), etc.

It is recommended that a POCT program should be developed and it has been suggested that the ideal POCT program should comprise the following features: (20)

(a) A formal training program, including regular re-training
(b) Ongoing competency assessment

Ensuring that:

- Testing is only performed by trained operators
- There is adequate and appropriate quality control program
- All documentation including user manual, quality control policies and other relevant policies should be made freely available for the operator
- There is regular and appropriate maintenance of POCT devices
- There is appropriate documentation of QC and patient results
- There is an audit trail from POCT request through to the results entered into patient notes
- There is a laboratory contact for advice or troubleshooting

The ideal POCT device would benefit to have the following features:

- Low cost
- Small, robust, lightweight and easily transportable
- Minimal maintenance and technical experience required
- Low sample volume and preferably whole blood sample type
- Simple and automatic calibration
- Easy QC operation with lockout if QC is unacceptable
- Data transfer capability, ideally with printout function and compatible with the main laboratory information services (LIS)
- Positive sample identification, preferably by barcode reading facility
- User ID and lock out features
- Be able to document any problems
- Have a communication system for remote access so that the laboratory can access the POC device for remote calibration, maintenance, quality control, and perform any troubleshooting necessary
- Rapid results that are in agreement with an accepted "Gold Standard"

Sample type is an important consideration. Whole blood analysis decreases response time by eliminating the need for specimen centrifugation and other pre-analytical steps. As a result, it facilitates medical decisions during life threatening crisis and emergency resuscitation when results may be required rapidly. Use of whole blood also enables blood conservation and helps minimise the necessity of blood transfusions that is especially important in the critically ill, paediatric and neonatal patients. Clinicians and users of POCT technology need to be aware of the possibility of the difference in reference intervals between the device and the laboratory, especially when using whole blood as sample type.

Types of POCT devices

There are a variety of POCT devices ranging from larger transportable analysers to hand held meters to miniature sensors. The transportable analysers carry a broad test menu and allow customisation of testing on a single sample. They utilize various specimen types, tend to be large and heavy, and thus are designed for bench top or mobile carts. Calibration is usually automatically performed periodically. They tend to be maintenance free, requiring only the occasional replacement of reagents and buffers. They often have data management systems that can download patient details, operator details, and results into the

hospital or laboratory information system. Smaller portable analysers such as the Reflotron® make use of disposable cartridge / cuvettes that have electrodes / sensors. Reagents are built into test strips and therefore the menu depends on the cartridge selected. They can be equipped with data management systems. Handheld devices such as glucose and prothrombin meters are highly mobile, use whole blood, and are found throughout hospital wards, clinics, and in the home. They use dry reagent technology, which is activated on contact with sample, and the data may be downloadable. They are highly dependent on operator technique. Immunodetection units involve testing for antibody or antigen, such as cardiac markers, HCG and PSA. Results are usually qualitative but in some cases can be quantified with a special reader.

Ex-vivo and in-vivo monitors have the potential for continuous and frequent monitoring. Sensors or electrodes are housed either externally to the patient or in micro porous tubing in an indwelling vascular catheter. These are advantageous for continual monitoring of critically ill patients, especially neonates and paediatric patients where the sample volume available for testing is low. Newer technologies include non-invasive devices that monitor the patient without the need for blood collection. For example, the Glucowatch" allows measurement of glucose transcutaneously using reverse iontophoresis and generation of an electrochemical signal, while the BiliChek" measures bilirubin transcutaneously using multi-wavelength spectral analysis.

POCT in the community

Currently POCT in the community is not regulated. Tests for the detection of HCG, urine ketones, and breath ethanol are available over the counter. Pharmacies are offering PSA, cholesterol, glucose, and *Helicobacter pylori* testing. The implications of this type of testing need to be considered. What guarantees are there that the tests are being performed correctly? Who is responsible for interpretation of the results? Is that individual "qualified" or competent to offer that interpretation? What is the significance of an abnormal result? Is QC performed?

Analytical performance is easily evaluated in the laboratory environment, but this does not give any information about the performance of the test in the non-laboratory environment. The evaluation of a point-of-care device needs to occur in the non-laboratory environment before ascertaining the minimum quality control requirement. du Plessis and colleagues assessed the analytical quality for glucose and total cholesterol performed in 12 randomly selected pharmacies in Pretoria, South Africa (21). They also evaluated the analytical performance of the 8 laboratory analysers that serviced the region. Part of the study involved volunteers visiting each pharmacy for glucose and cholesterol testing. They also had the same tests performed by the laboratory after the pharmacy visit. The larger analytical variability for the tests carried out in the pharmacies when compared with the laboratories was thought to be contributed to by the lack of internal quality control, external quality assessment, as well as non-uniformity of calibration and deficiency in training.

A five-year study in Denmark led to a formalised Quality Assurance program for POCT (22). In 1992, the first testing round showed that none of the instruments in the general practice surgeries complied with the laboratory criteria of +/- 20% total error. Involvement from the diagnostics companies to improve analysers, training and manuals, and visits to the general practices by a technologist led to much improvement in the second round of testing in 1994. This program prompted general practitioners to improve procedures for handling patients, specimens and testing. Many also requested assistance from laboratory. In 1996, it was shown that the previous improvement in the quality was maintained.

A recent Australian review of the role and value of near patient testing (NPT) in the general practice gave the following recommendations (23):

- Technical and practical performance indicators of NPT devices based on structured and appropriate assessment is essential
- A classification of tests for accreditation purposes is essential
- A NPT practice accreditation process is essential and it should be conducted jointly by the Royal College of Pathologists of Australasia (RCPA) and the Royal Australian College of General Practitioners (RACGP)
- A system of partnership between pathology laboratories and general practice is desirable
- External quality assurance program for each NPT needs to be established
- Evaluation of clinical effectiveness is essential
- Evaluation of the impact that NPT has on the health care system is desirable
- CME on the underlying principles and the quality use of tests is desirable
- Funding and support of research on NPT is fundamental from the industry and from the government research funding organisations
- A structure providing national guidelines on the use of NPT is desirable
- Reimbursement of NPT in general practice should be at a level that would not favour under or over-servicing but good quality use of tests
- The method of payment should not increase social inequities to access to care
- Current accreditation costs should be reduced as they discourage the quality use of NPT
- If a GP pathology laboratory partnership solution is favoured, the financial agreement between them should foster good practice, limit under and over-servicing and encourage harmonious professional relationship

Implementing these guidelines along with the ISO/WD 22870, in the community will go a long way towards improving the current situation, especially in New Zealand where, I suspect there is a lack of control of POCT in the community environment.

This community laboratory experience with POCT in a non-laboratory site has been an interesting experience. A lot of patience is required when training non-technical staff. The situation is aggravated by high staff turnover. The different culture and expectations between non-laboratorians and technical staff need to be addressed. Documentation and quality control appear not to be priorities for non-laboratory staff, whereas a quality result is highly dependent on these factors along with proper maintenance and handling of POCT devices. The most important factor is open communication between all parties concerned.

Connectivity

Another issue to consider is data management of the results obtained from POCT devices. It is important that not only are the results available in real time, especially for critical care environments, but that the results are available in the patients' records. Blick found that as little as 10% of POCT results are managed by the central laboratory computer system (24). This is possibly due to the cost and technical problems of interfacing these devices into the laboratory computer system. With some POCT, hard copies of results are not even available. This brings about its own problems. There is no traceability of the result and transcription of results is a major concern. Devices that rely on the operator to record this information are fraught with ongoing issues of mislaid results, transcription errors, billing issues and the like. The ideal

POC device should have the capability to electronically transfer the required information into the patient record, laboratory information system (LIS) or other system. The issue with this is that there are many soft / hardware platforms, and many devices are not compatible. The use of 'plug in and play' devices where the device can be hooked into any port and download to any system would be ideal. Thus, a single data management system should have the ability to communicate with all devices no matter what type of device or who the manufacturer is.

This is where the new connectivity standard will come into play. Connectivity is the integration of the patient results and supporting data with the patient records. A group of industry manufacturers, organisations and health providers formed the Connectivity Industry Consortium (CIC) and developed the NCCLS POCT1-A Point of Care Connectivity Approved Standard. The idea behind this was to formulate a set of standards for companies to work with that is common to all POC devices, information management systems and communication networks. The advantage to users in the future is that the devices should hook into their information system (once it also complies with the standard) and there will be no need to have proprietary interfaces and the associated cost.

To comply with this standard, POC devices must be able to download data electronically to the host. Remote access will enable the laboratory to access QC files, calibration, and statistics and also to troubleshoot. Operator use of barcode and / or passwords enables compliance checking and operator lockout if required. Other communication options for transfer of data include cell phones, personnel digital assistants (PDA) and the Internet. However, whatever communication system is used, it must be highly reliable, available at all times and the data must be secure.

Byrdy and colleagues reported on a survey conducted by the Enterprise Analysis Corporation (EAC) of 20 venders of hospital POC devices and data management systems to access progress in implementation of the POCT -1A standard (25). Five vendors at that time were offering devices that were POCT-1A compliant and all the vendors surveyed that had products in development intended to incorporate the standard into most, if not all new products. The survey discovered that >20% of current devices provide no connectivity capability. A recent survey of hospitals conducted in 2001 by the EAC showed that 57% of POC results were not captured and 31% were transferred electronically. Compare this with the 1999 survey results of 67% not captured and 16% electronic transfers. Venders, responding to the vendor survey, reported that they are not expecting to apply the standard to existing products, preferring to focus on new generations of products. Interestingly, the vendors commented that many customers were not yet familiar or aware of the POCT connectivity standard.

Recent Developments

Anyone who has had to undergo regular blood tests or has had to witness a baby undergoing multiple heel pricks will tell you that non invasive techniques for testing and monitoring is the preferred option. Minimal or non-invasive devices are being developed. In the late 1990's the use of a continuous arterial blood gas monitoring system became available. This technology was based on the combination of optochemical and fibre optic detectors measuring pH, pCO2, pO2 and temperature on a continuous basis via a sensor placed in an artery (26). Weiss and colleagues conducted an evaluation on this technology on paediatric patients (27). Twenty-four patients with a mean age of 6.4 years had a sensor placed through a standard 20 gauge arterial catheter. In the study 24% had technical problems of various sorts. These included sensors being accidentally being pulled out, or kinked during patient movement or positioning because the tip of the sensor extended out past the catheter, sensors in the wrong position, or sensors being exposed to too much ambient light, such as heating lamps. Progress led to the development of an ex-vivo in-line blood gas and electrolyte monitor. This device could be directly connected to the patient via an arterial catheter. Six sensors contained in a fluid-filled, thermostatically controlled flow cell at body temperature were contained in a closed system connected directly to the arterial catheter. The sensors used electrochemical and ion-selective electrodes and electrical conductance for determining blood gas and electrolytes measurements. A stopcock is part of the system for directing the flow of parenteral fluids and blood samples. Sample was diverted through the flow cell, analysed, and then returned back to the patient via the catheter. Widness and colleagues evaluated the system that had been developed for paediatric patients (28). Sixteen neonates were monitored for a total of 37 days. The mean sample loss was 24.7 µL compared with 250 µL for conventional blood sampling. Billman and colleagues conducted a similar study involving 100 critically ill neonates and infants across seven children's hospitals (29). There are many advantages of this technology, the main one being the lower blood volume loss, which for an infant means less likely requirement for erythrocyte transfusion.

Other minimally and non-invasive technology being developed include near-infrared radiation (NIR) transmission. This involves illumination of a spot on the body with low-energy NIR light causing the light to be partially absorbed and scattered according to its interaction with chemical components within the tissue, before being reflected back to the detector. Monitoring of blood glucose by diffuse reflectance over the 1050 - 2450nm wavelength range has been demonstrated (30). The tongue, having a low fat content, is the area of choice according to Burmeister and Arnold (31). Substantial research is required though to determine whether NIR is viable as a measurement system for glucose testing.

Orthogonal polarization spectral (OPS) imaging is a method that uses reflected light in a unique way to digitally visualize and analyse the microcirculation blood vessels. This process allows for individual micro vessels and blood cells to be backlit thus allowing the application of Beers Law to vessel contents. Hemoscan is one such device that uses a probe placed under the tongue. It is attached to a special computer and uses imaging of the micro vessels and algorithms to compute the components of a blood count. BiliChek by SpectRx uses multi-wavelength spectral analysis for measuring bilirubin transcutaneously. The intensity of light reflected back from the skin after illumination by the device is measured. This minimises the necessity of multiple heel pricks.

For diabetic patients that are on insulin, hypoglycaemia is a major concern, especially at night. The availability of a device that constantly monitors the glucose levels and alarms when an impending hypoglycaemic episode is about to occur will relieve some of the stress that this condition causes. The GlucoWatch®G2™ Biographer was approved for use by the United States Food and Drug Administration in 2002. This is a watch like device worn on the wrist and monitors the persons glucose readings continuously and automatically. The device measures glucose that is extracted through intact skin by reverse iontophoresis. A low voltage electric current is applied to the skin that induces an electro-osmotic flux of glucose that is collected in a hydrogel and analyzed on a platinum-carbon composite electrode. The Biographer contains an alarm that alerts the wearer to treat an impending 'hypo' before a severe episode occurs. Garg and colleagues evaluated the use of the GlucoWatch®G2™ Biographer on young people with Type 1 diabetes in 1999 (32). Seventy-six Biographers were evaluated in a controlled outpatient setting as well as in the home setting for 3 days. The Biographer, once calibrated, was able to give glucose results as frequently as one every 20 minutes. The

results correlated well with the corresponding finger prick glucose values although it was shown that the Biographer had a lag time of 17 minutes. The devices caused mild oedema and erythema but these were not a major deterrent in accepting the device. When asked, 80% of the subjects evaluating the device would like to have it to assist in their management of diabetes. Pitzer and colleagues conducted a larger evaluation of more than 1000 Biographer uses from four clinical trails over a large and demographically diverse patient population in controlled and normal daily environments with similar results (33). Both studies concluded that the use of a Biographer or similar device, that continuously or very frequently monitor glucose levels, will be of great benefit to diabetic patients particularly those at risk of hypoglycaemia. These are just a few of the new technologies being investigated.

Regulatory requirements

In the United States, all laboratory testing, including POCT must abide by the Clinical Laboratory Improvement Amendments (CLIA). All sites must operate under one of three CLIA certificates. These certificates are based on the complexity of the testing. Waived tests are the least complex and do not require the stringent regulations that cover the rest of the testing. These tests are ideal for use in the home environment. Guidelines for implementation of POCT are available including those issued by the NCCLS and IFCC (34). It is important that professional standards are set and maintained, not only for the sake of the laboratory profession, but also for the protection of the public and patients (35 - 37).

In 2004 all New Zealand medical laboratories will be assessed under the new ISO15189 standard. ISO/WD 22870 Clinical Laboratory testing - a Guidance Document on the Application of EN ISO 15189 to Point of Care Testing is currently a draft document but that will apply to hospital and clinics (38). Patient self-testing in a home or community setting is excluded under this draft. Under the 22870 guidelines, the hospital laboratory will become responsible for hospital POCT. Some requirements for medical laboratory accreditation will also apply to the POCT environment, such as training and competency records, quality control, calibration, and maintenance. Although this maybe a welcome change, it is going to be a logistical and financial nightmare. How far should the regulatory requirements be taken? For example, do we really need to have competency records for urine dipsticks?

The laboratory needs to take responsibility of the test results irrespective of where the test is performed. Yap (39) states, *"The Central Laboratory must assume full control of POCT to ensure the quality of the analysis."* Responsibilities include:

- Determine which test warrant POC status
- Evaluate whether the instrument selected is appropriate
- Establish and implement testing procedure
- Training and education of operators
- Taking charge of instrument maintenance
- Maintaining stock control
- Review and evaluation of QC
- Maintenance of complete records of patient results
- Implementation of critical value policies
- Monitoring compliance with the POCT policies and procedures.

In the hospital environment, I would agree. But is this practicable in the community environment?

Evaluation of use of whole blood specimen for Reflotron®.

Methods and materials

A single point of care analyser (Roche Reflotron®, Roche Diagnostics, Mt Wellington, Auckland, New Zealand) with one operator was used within the laboratory environment for the duration of the project.

For potassium, the detection reaction takes place in a non-polar water-insoluble phase that contains valinomycin, a pH indicator and an organic acid. The valinomycin acts as an ion-selective membrane. The intensity of the color change of the pH indicator is a measure of the potassium concentration in the sample and is monitored by means of reflectance photometry at 642nm. The analysis takes approximately 140 seconds. The Reflotron® potassium method is calibrated against the flame photometry method.

In the glucose assay, D-glucose in the sample is oxidised to (-D-gluconolactone in the presence of glucose oxidase. The hydrogen peroxide formed then oxidises the indicator 3,3',5,5'-tetra-methybenzidine (TMB) in the presence of peroxidase (POD). The intensity of the colour formed is proportional to the glucose concentration in the sample and is measured by reflectance at 642nm and takes approximately 140 seconds. The recommended sample type for glucose is serum, plasma, fresh capillary or venous whole blood.

Our specimen of choice for use on the Roche Reflotron(analysis is serum. In order to obtain sufficient material for this preliminary study, 20 apparently healthy volunteers donated 20 ml of blood. Blood was collected into tubes containing potassium EDTA and lithium heparin as anticoagulant and into a plain serum tube (Becton Dickinson) in the following order: plain, lithium heparin, potassium EDTA.

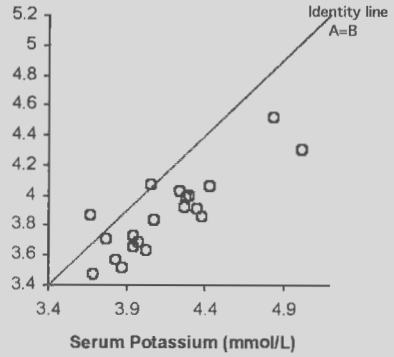
Haematocrit was measured on the EDTA sample using a Coulter SKTS. The lithium heparin samples were well mixed and potassium and glucose were measured on the Reflotron(within 30 minutes. After analysis of the lithium heparin whole blood, the samples were centrifuged at 3500 rpm for 7 min, after which the plasma was analysed for potassium and glucose on the Reflotron(. The plain samples were allowed to clot for 30 min before being centrifuged. Potassium and glucose were measured on the serum within one hour. Precinorm Reflotron® control was used for the purpose of controlling the assays.

Ten replicate measurements of one sample for potassium and glucose were used to estimate intra- assay imprecision. Inter-assay imprecision was estimated by analysing frozen aliquots of separated lithium heparin plasma and serum over a ten-day period.

Data was entered into a Microsoft Excel spreadsheet and was used to calculate the imprecision, coefficient of variation and means. Comparison of means for potassium and glucose for each sample type was achieved using the paired t-test in Analyse-It. Analyse-It was also used to prepare linear regression and bias plots.

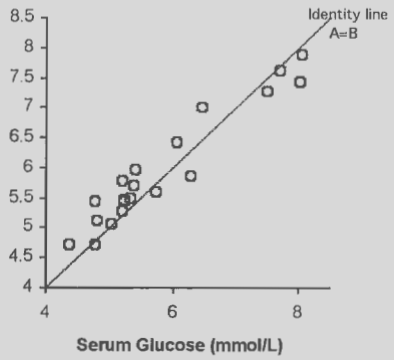
Results

Sample concentrations for glucose were in the range 4 - 8 mmol/l with a serum mean of 5.83 mmol/L, standard deviation (sd) of 1.14, and whole blood mean of 5.97 mmol/L, sd of 0.97. Sample concentrations for potassium were in the range 3.4 - 4.8 mmol/l with a serum mean of 4.14 mmol/L, sd of 0.35, and whole blood mean of 3.87 mmol/L, sd of 0.26. Linear regression analysis for potassium: whole blood potassium = 0.628 x serum + 1.265, r = 0.85; and for glucose was: whole blood glucose = 0.82 x serum + 1.186, r = 0.96 (Figures 1 and 2).



y=0.628x + 1.265; r=0.85

Figure 1. Linear regression. Lithium heparin whole blood vs serum - potassium



y=0.82x + 1.186; r=0.96

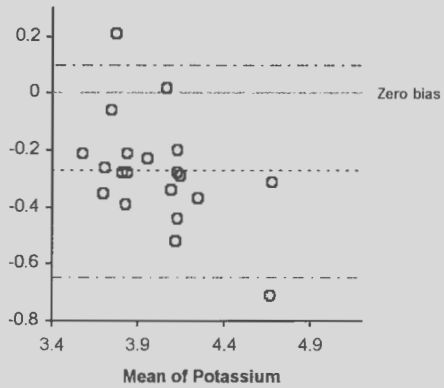
Figure 2. Linear regression. Lithium heparin whole blood vs serum - glucose

Bland and Altman analysis of the potassium data gave a mean difference between serum and lithium heparin whole blood of -0.275 mmol/L, sd: 0.185 mmol/L. For glucose the mean difference was 0.137 mmol/L, sd: 0.33 mmol/L (Figures 3 and 4). This difference between means was not statistically significant for glucose, p=0.0867); but was for potassium, p= <0.0001 (Table 1). Mean haematocrit was 0.398, range: 0.364 - 0.435 (Table 1).

Test (n=20)	Concentration range (mmol/L)	Mean difference serum /whole blood (95% CI)	p value
Potassium	3.4 to 4.8	-0.275 (-0.365 to -0.185)	<0.0001
Glucose	4.0 to 8.0	0.137 (-0.022 to 0.296)	0.0867

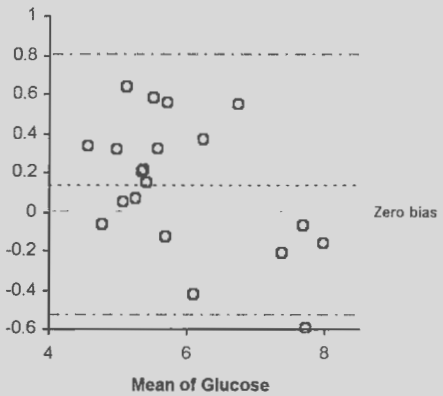
For the purpose of this study, no data was excluded.

Table 1. Difference between the means for serum and whole blood analysis



Calculated mean (d) = -0.28 mmol/L; 2s(d) = 0.37 mmol/L

Figure 3. Bland and Altman bias plot. Lithium heparin whole blood vs serum



Calculated mean (d) = 0.14 mmol/L; 2s(d) = 0.66 mmol/L

Figure 4. Bland and Altman bias plot. Lithium heparin whole blood vs serum glucose

Within day imprecision (CV) for whole blood was 1.1% for potassium and 1.6% for glucose (n=10). For serum, this imprecision was 0.8% and 2.7% respectively, and for plasma 1.3% and 1.9% respectively (Table 2).

Specimen and Type (n=10)	Potassium (mmol/L)		Glucose (mmol/L)	
	Mean	%CV	Mean	%CV
Lithium Heparin Whole Blood	3.57	1.10	5.43	1.63
Lithium Heparin plasma	3.60	1.26	5.76	1.93
Serum	3.84	0.81	5.22	2.69

Table 2. Intra-assay coefficient of variation

Between day imprecision (CV) was 1.7% for serum potassium and 1.9% for serum glucose (n=10). For plasma, this was 1.7% and 2.4% respectively. Values obtained using Precinorm quality control were 2.3% for potassium and 2.5% for glucose (Table 3).

Specimen and Type (n=10)	Potassium (mmol/L)		Glucose (mmol/L)	
	Mean	%CV	Mean	%CV
Lithium heparin plasma	3.68	1.65	5.85	2.36
Serum	3.80	1.73	5.36	1.92
Roche Precinorm QC	3.61	2.28	6.41	2.51

Table 3. Inter-assay coefficient of variation

Previous intra-assay imprecision studies on this Reflotron" had given the following results for serum:

Glucose	Level 1 (mean 5.87) = 1.69%	Level 2 (mean 18.46) = 2.23%	n=20
Potassium	Level 1 (mean 4.35) = 1.51%	Level 2 (mean 6.50) = 1.70%	n=20

Discussion

The Roche Reflotron® is a "dry chemistry" system that analyses a variety of biochemical analytes using reflectance technology. Test and batch information, along with calibration and operational instructions are stored on a magnetic strips located on the reagent test strip. Changes in the performance of different batches of strips are encoded on the strip and the analyser does not require any setting changes. The sample (30 µl serum, plasma or whole blood) is applied via a pipette to the sample zone (mesh). The sample diffuses evenly into the different layers. In assays where whole blood is an acceptable sample type, plasma is separated from the cellular material by glass fibres. These fibres screen out the erythrocytes and other cellular constituents. The sample is carried by capillary action to the reaction zone that contains the necessary reagents to allow the analytical process to proceed and to produce a colour change. The water content of the sample is sufficient to hydrate the dry reagents and enable the chemical reaction to occur. The concentration of the analyte is calculated from the measurement of the intensity of the reflected light reflectance at a specific incident wavelength. The variety of reagent strips available enables great flexibility of test menu. Thus the Reflotron® can be utilised in a variety of situations from GP surgeries to retail pharmacies. The analyser does not require calibration but does require very minimal maintenance. It is, in effect, a very simple analyser to use.

The hypothesis for this pilot study was that whole blood could be used for glucose and potassium measurement on the Reflotron® and thus the necessity for sample centrifugation could be eliminated. Unfortunately, the study was not sufficiently well designed to categorically prove this hypothesis to be true. The sample size was too small and the range of values too narrow. It did, however, show that whole blood sample type for potassium analysis is not likely to be suitable ($p<0.0001$). There was insufficient data in this study to support the use of whole blood sample type for glucose. Even though the difference in mean glucose values was not statistically significant, the sample population size and analytical range again was too small to substantiate this result. However, the difference observed is unlikely to be clinically significant in the setting in which the analyser is likely to be used. It will be necessary to conduct further studies looking at a wider range of values with a larger sample size as well as a range of clinical diagnosis to determine whether whole blood is an option for specimen sample type on the Reflotron®.

A potential problem with measuring whole blood potassium is that haemolysis is not detected by the POCT analyser. Haemolysis of samples often leads to spuriously elevated potassium values due to the leakage of cytoplasm into the plasma and thus could lead to misleading results, misdiagnosis or inappropriate treatment. Hawkins assessed the prevalence of haemolysed specimens when analysing whole blood samples on an AVL Omni 6 blood gas analyser (40, 41). Five hundred and fifty samples were assessed for haemolysis using the haemolysis index on a Hitachi 917. This showed that 18% of samples were haemolysed to some degree. When the haemolysis effect was estimated, by use of a potassium / haemoglobin (K/Hb) ratio, 22% of the normokalemic samples were downgraded to hypokalemic, 8% of hyperkalemic samples became normokalemic and 6% of hyperkalaemic samples became hypokalemic. Hawkins concluded that haemolysis correction is not recommended in clinical practice using the K/Hb ratio, that the magnitude of haemolysis in whole blood samples is approximately 18% (particularly with low volume samples), and questioned whether whole blood sample for potassium measurement should be used at all. Roche does not recommend whole blood analysis for measuring potassium on the Reflotron®. However, as potassium is one of the most common tests performed on the Reflotron®, I felt it would be useful to measure any difference between our current recommended sample type (serum) and a whole blood sample.

Imprecision was satisfactory according to our laboratory arbitrary value of a CV < 5%. Even though only 10 replicates were used (instead of the standard minimum number of 20), the results were similar to previous studies conducted on the same analyser. Results were also similar to other reported values (42, 43). The Roche package insert gives within day and between day imprecision values for glucose between 2 - 4% and for potassium of 0.7 - 1.3%. Nanji and colleagues evaluated the Reflotron® for a number of analytes, including glucose, in 1987 and obtained the following results (mean glucose value in parenthesis): within run imprecision (n=20) 2.2% (5.49 mmol/L) and 1.6 % (11.87mmol/L). Between run values for glucose was 2.6% (5.87mmol/L) and 1.9% (12.2 mmol/L). Potassium was not evaluated in this study (42). Ng and colleagues evaluated the use of plasma and serum potassium on the Refotron® in 1992 and obtained within day imprecision (n=20) of 1.0% for patient value of 3.6 mmol/L, 1.0% for control value of 5.6mmol/L and 1.2% for control value of 6.4mmol/L (43). Between run imprecision (n=20) values of 1.0 - 1.1 % for control values 3.6, 5,5 and 6.5mmol/L. A search of the medical literature failed to reveal any studies investigating the use of whole blood as specimen type in the measurement of potassium on the Reflotron®.

A well-designed study should have the resources to evaluate the analytes over the whole analytical range for the assay using paired sample measurements. The use of power calculation before designing such a study is beneficial in determining the sample size needed to prove or disprove the hypothesis. Further design of the study to include patient outcomes would support the implementation of POC if it were warranted. Since the completion of this study, the Reflotron® has been removed from the surgery and moved to a nearby satellite laboratory where trained laboratory staff members are responsible for its use. The need to use whole blood as a sample type thus did not eventuate.

Benefits	Potential Problems
Shorter TAT or TTAT	Possible inferior test performance
Minimised transport costs	Large number of operators, staff turnover.
Patient satisfaction - quicker treatment and/or fewer physician visits necessary	Inadequate maintenance and quality control.
"Ownership" of result at POCT site.	Lack of understanding of QC issues
Potential decreased length of stay in hospital or department	Increased running costs (duplication of testing, I higher cost of POCT supplies.)
Enhanced clinical management - better monitoring of certain chronic conditions.	Possible discrepancies of results between POCT and laboratory.
Closer doctor/patient relationship.	Possible discrepancies of reference ranges
Direct discussion of result with patient.	Consequence of an incorrect result.
Improved therapeutic control	Data management - lack of results in patient files.
More rational prescribing	
Small sample volume.	Increase usage of calibrations and controls per test.
Convenience.	Possible increase in cost per test
Decrease pre-analytical errors	
	Quality of sample eg whole blood can mask issues like haemolysis / lipaemia
	Additional nursing tasks
	Lack of traceability

Table 4. Benefits and Issues of POCT Implementation

Conclusions

The use of whole blood for glucose has been evaluated many times over in the past on various devices and is in general an accepted practice. Roche, however, do not recommend whole blood for measurement of potassium on the Reflotron®. This study showed a difference of -0.275 mmol/l between serum and potassium whole blood analysis.

A whole blood sample is the preferred specimen of testing in the general practice. This reduces the turn-around-time for results by eliminating the need to centrifuge the sample. If the medical centre running the instrument decided to consider the use of whole blood for sample analysis to decrease the turn around time, the laboratory would advise strongly against measuring whole blood potassium. This would then lead to the dilemma as to whether the TAT is critical for measuring potassium or whether they can wait 10 min to centrifuge a lithium heparin specimen. There are very few situations where a general practitioner cannot wait 10 min for a potassium result. With serum, there also is a time requirement for clotting.

In this study there was insufficient data to conclusively support a change in sample type from serum to whole blood for glucose but there is evidence that whole blood sample is not suitable for potassium. If the practice was keen to further evaluate the feasibility of using a POCT analyser, a more thorough evaluation would be required, using a larger range of samples across a greater spectrum of analyte values and encompassing all the analytes deemed important by the practice.

Implementation of POCT is not always appropriate or practical. If the perception is that it takes too long to perform the test or that the equipment is too difficult to operate, then the analyser will not be utilised to the extent that it could be. By changing the sample type and thus potentially decreasing the TAT, it is hoped that the usage would increase. Along with the increased usage comes familiarity, hopefully a change in culture, acceptance and appreciation of the value of quality assurance leading to minimal problems associated with non-use and lack of familiarity.

It is critical to have an adequate program when implementing POCT at sites. This should include training and on-going education, a quality assurance program and access to lab personnel for troubleshooting. Regular review of all aspects, possibly by regular auditing but definitely by regular quality control review should be strongly encouraged. Obtaining an "on board" attitude by the staff performing the POCT testing is essential to have an effective process. It is advisable to have a POCT team that has representatives from all the potential stakeholders. It is their responsibility to evaluate the POCT requirements, develop policies and procedures, and organise training, set-up quality control procedures and reviews and act as overseers. POCT is here to stay, thus we need to look at ways to make this process as cost effective and trouble free as possible.

Will POCT be a threat to the laboratory? We should not feel threatened, as there is the opportunity for the scientist / technologist to be consultant / advisers and to further enhance the essential value of the work we do. We have a great opportunity to work in conjunction with general practitioners and pharmacies to implement POCT sites, to be educators, coordinators, offer advice and support; supervise training and on-going competency, organise quality assurance programs, perform maintenance, service and quality control checks and assist with troubleshooting. We need to have a voice in decision making so that the most appropriate and cost effective strategies are introduced. Surely, a co-operative environment would best benefit the patient.

The way forward for our laboratory in future is to include a fuller evaluation of the use of whole blood for all analytes, with the exception of potassium. We need to audit the use of the POCT device, including the impact that it has on the patient outcome. in conjunction with this, a quality assurance program should be put in place. If the review shows that the result on patient outcome is minimal, then a complete review as to why the POCT device is in place should be considered, although ideally this should have occurred before the device was put in place.

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References

1. Collinson PO. The need for a point of care testing: an evidence-based appraisal. *Scand J Clin Lab Invest Suppl* 1999; 230: 67-73.
2. Jacobs E. Is point-of-care testing cost effective? *Clin Lab News* 1996. http://www.aacc.org/cln/features/96features/poct.html
3. Brogan GX Jr, Bock JL. Cardiac marker point-of-care testing in the Emergency Department and Cardiac Care Unit. *Clin Chem* 1998; 44: 1865-9.
4. Dahler-Eriksen BS, Lauritzen T, Lassen JF, Lund ED, Brandslund I. Near-patient test for C-reactive protein in general practice: assessment of clinical, organizational, and economic outcomes. *Clin Chem* 1999; 45: 478-85.
5. Piironen T, Nurmi M, Irjala K, Heinonen O, Lilja H, Lovgren T, et al. Measurement of circulation forms of prostate-specific antigen in whole blood immediately after venipuncture: implications for point-of-care testing. *Clin Chem* 2001; 47: 703-11.
6. Diabetes Point of Care. 2001. http://www.pointofcare.net/clinical/diabetes/DiabetesIndex.htm
7. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Engl J Med* 1993; 329: 977 - 86.

8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1999; 352: 837-53.
9. Aubert RE, Herman WH, Waters J, Moore W, Sutton D, Peterson BL, et al. Nurse case management to improve glycemic control in diabetic patients in a health maintenance organization. *Ann Intern Med* 1998; 129: 605 - 12.
10. Kendall J, Reeves B, Clancy M. Point of care testing: randomised controlled trial of clinical outcome. BMJ 1998; 316: 1052-7.
11. Nichols JH, Kickler TS, Dyer KL, Humbertson SK, Cooper PC, Maughan WL, et al. Clinical outcomes of point-of-care testing in the interventional radiology and invasive cardiology setting. *Clin Chem* 2000; 46: 543-50.
12. Lee-Lewandrowski E, Corboy D, Lewandrowski K, Sinclair J, McDermont S, Benzer T. Implementation of a point-of-care satellite laboratory in the emergency department of an academic medical center. Impact on test turnaround time and patient emergency department length of stay. *Arch Pathol Lab Med* 2003; 127: 456 - 60.
13. Weitgasser R, Gappmayer B, Pichler M. Newer portable glucose meters - analytical improvement compared with previous generation devices? Clin Chem 1999; 45: 1821-5.
14. Handorf CR. Quality control and quality management of alternate-site testing. *Clin Lab Med* 1994; 14: 539-57.
15. Narayanan S, Guder WG. Preanalytical variables and their influence on the quality of laboratory results. e*JIFCC* 2002; 13 . http: //www.ifcc.org/ejifcc/vol13no1/1301200107.htm
16. Scott MG, Kucik DF, Goodnough LT, Monk TG. Blood substitutes: evolution and future applications. Clin Chem 1997; 43: 1724-31.
17. Moreira PL, Lansden CC, Clark TL, Gawryl MS. Effect of Hemopure on the performance of Ektachem and Hitachi clinical analyzers. *Clin Chem* 1997; 43: 1790-2.
18. Le Grice J. Near patient testing? NPT - non professional testing? Non patient testing? Med Tech International 1994; No.1: 9-10.
19. Goldsmith BM. Point-of -care testing. How laboratorians can ensure quality beyond the lab. *Clin Lab News* 2001. http://www.aacc.org/cln/features/01/features/apr01feat.htm
20. Crook MA. Near patient testing and pathology in the new millennium. *J Clin Pathol* 2000; 53: 27-30.
21. Du Plessis M, Ubbink JB, Vermaak WJ. Analytical quality of near-patient blood cholesterol and glucose determinations. *Clin Chem* 2000; 46:1085-90.
22. Stahl M, Brandslund I, Iversen S, Filtenborg JA. Quality assessment of blood glucose testing in general practitioners' offices improves quality. *Clin Chem* 1997; 43: 1926-31.
23. Guibert R, et al. Review of the role and value of near patient testing in general practice. Report to the Pathology Section Diagnostics and Technology Branch. *Commonwealth Department of Health and Aged Care*; Nov 1999.
24. Blick KE. The essential role of information management in point-of-care/critical care testing. *EIFCC*; 12 (4). http://www.ifcc.org/ejifcc/vol12no4/vol12no4a1.htm
25. Byrdy P, Mappes R, Stephans E. Point of care connectivity standard. Progress in compliance. *Point of Care* 2003; 2: 39 - 48.
26. Zollinger A, Spahn DR, Singer T, Zalunardo MP, Stoehr S, Weder W, et al. Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery. *Br J Anaesth* 1997; 79: 47-52.
27. Weiss IK, Fink S, Harrison R, Feldman JD, Brill JE. Clinical use of continuous arterial blood gas monitoring in the pediatric intensice care unit. *Pediatrics* 1999; 103: 440-5.
28. Widness JA, Kulhavy JC, Johnson KJ, Cress GA, Kromer IY, Acarregui MJ, et al. Clinical performance of an in-line point-of-care monitor in neonates. *Pediatrics* 2000; 106: 497-504.
29. Billman GF, Hughes AB, Dudell GG, Waldman E, Adcock LM, Hall DM, et al. Clinical performance of an in-line, ex vivo point-of-care monitor: a multicenter study. *Clin Chem* 2002; 48: 2030-43.
30. Malin SF, Ruchti TL, Blank TB, Thennadil SN, Monfre SL. Noninvasive prediction of glucose by near-infrared diffuse reflectance spectroscopy. *Clin Chem* 1999; 45: 1651-8.
31. Burmeister JJ, Arnold MA. Evaluation of measurement sites for noninvasive blood glucose sensing with near-infrared transmission spectroscopy. *Clin Chem* 1999; 45: 1621-7.
32. Garg SK, Potts RO, Ackerman NR, Fermi SJ, Tamada JA, Chase HP. Correlation of fingerstick blood glucose measurements with GlucoWatch Biographer glucose results in young subjects with type 1 diabetes. *Diabetes Care* 1999; 22: 1708-14.
33. Pitzer KR, Desai S, Dunn T, Edelman S, Jayalakshmi Y, Kennedy J, et al. Detection of hypoglycemia with the GlucoWatch Biographer. *Diabetes Care* 2001; 24: 881-5.
34. Freedman DB. Guidelines for implementation of point of care testing. *IFCC Publication*.
35. Ehrmeyer S. US legislation for decentralized testing. *Blood Gas News* 1999; 8: 20-6.
36. Ehrmeyer SS, Laessig RH. Application of the Department of Health and Human Services proposed waived status requirements for in vitro diagnostic testing devices: case study. *Clin Chem* 1997; 43: 1610-7.
37. Position Paper (Final). Point of care testing. American Society for Clinical Laboratory Science. Updated 10/96. http://www.ascls.org/position/point.htm
38. ISO/WD 22870 clinical laboratory testing - a guidance document on the application of EN ISO 15190 to point-of-care testing (POCT). Draft document. *NCCLS*; May 2002.
39. Yap C. Quality assurance in 'point of care testing'. *Med Tech International* 1994; No.1: 4-5.
40. Hawkins R. Measurement of whole-blood potassium - is it clinically safe? *Clin Chem* 2003; 49: 2105-6.
41. Hawkins R. Variability in potassium/hemoglobin ratios for hemolysis correction. *Clin Chem* 2002; 48: 796.
42. Nanji AA, Sincennes F, Poon R, Hinberg I. Evaluation of the Boehringer Mannheim "Reflotron" Analyser. *Clin Chem* 1987; 33: 1254.
43. Ng RH, Sparks KM, Statland BE. Colorimetric determination of potassium in plasma and serum by reflectance photometry with a dry-chemistry reagent. *Clin Chem* 1992; 38: 1371-2.

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Comparative sensitivities and specificities of two rapid HBsAg detection methods and their relationship to a third generation commercial enzyme immunoassay

Paul M Austin MSc (Hons), DipMLT; Section Leader-Serology Unit, Department of Virology and Immunology, LabPlus, Auckland City Hospital, Auckland

Abstract

Objective Uses of rapid tests for HBsAg are part of an integrated (QA and diagnostic) approach in our laboratory for HBV serodiagnosis. Withdrawal from manufacture of a red cell agglutination method necessitated a replacement be found.

Methods Two commercial methods (Uni-Gold™ HBsAg from Trinity Biotech and Determine™ HBsAg from Abbott Laboratories) that had local distributors were available for evaluation.

Results Testing a panel of clinical sera demonstrated equivalent specificities; however, significant differences in assay sensitivity was noted. The method with the higher sensitivity (Determine™ HBsAg) is expected to be reactive when the Axsym™ HBsAg method has a sample-to-negative (S/N) ratio of 50 or greater. An interesting finding was that the Axsym™ HBsAg assay exhibits a non-linear response (i.e. saturation) when S/N ratios are greater than 200.

Conclusions We found that the format, speed of testing, ease of reading and sensitivity level of the Determine™ HBsAg method ideal for the range of uses as applied in our laboratory.

Keywords: HBsAg, Determine™ HBsAg, Uni-Gold™ HBsAg, Axsym™

Introduction

Hepatitis B surface antigen (HBsAg) is the envelope protein of Hepatitis B virus (HBV). The link between serum hepatitis and HBsAg was established by Prince in 1968 (1). The 'S' gene of HBV encodes three glycoproteins (small [S], middle [M] and large [L]) of HBsAg. The small glycoprotein is completely contained in the middle, which in turn is completely contained within the large glycoprotein. The glycoproteins encode three polypeptides [preS1, preS2 and S] (2). Apart from HBsAg being an essential component of the complete 42nm diameter virion (Dane particle), it is also found in non-infectious spherical (22nmdiameter) and filamentous (100-700nm long) forms in sera of infected individuals (2). HBsAg can be detected in the serum of infected individuals several weeks before and months after symptom onset. Additionally, HBsAg is present in the sera of chronically infected persons. It follows therefore that detection of HbsAg in serum is consistent with individuals being potentially infectious (3).

Our laboratory uses rapid HBsAg detection methods for three reasons. Firstly, as a quality assurance mechanism to check for possible errors in serum separation as we test serum aliquots as opposed to direct testing from primary tubes. Secondly, as a reportable diagnostic assay where specimen volumes are minimal and re-collections are either an inappropriate or impossible option (i.e. paediatric cases or patients with poor vein presentation due to long-term malnutrition or other clinical causes). Thirdly, it is used as a supplemental HBsAg method (i.e. HBsAg is detected by two different assays, where ideally each uses different operational principles). Supplemental testing for HBsAg has been chosen in our laboratory as an appropriate alternative to the standard approach of neutralisation for HBsAg confirmation.

The withdrawal from manufacture of a commercial rapid red-cell agglutination based assay (Agen SimpliRed™) for HBsAg detection required us to find a replacement. As well as establishing comparative performance between two commercial rapid methods, the situation also afforded us the opportunity to definitively establish the relationship (in terms of sensitivity) between the rapid assays and our primary automated diagnostic assay (Axsym™ HBsAg version 2.0).

Materials and methods

Rapid HBsAg assay methods

Two commercial assay systems (Determine™ HBsAg and Uni-Gold™ HBsAg) were provided to the laboratory for evaluation. The Determine™ HBsAg and Uni-Gold™ HBsAg assays are manufactured by Abbott Laboratories and Trinity Biotech respectively.

Both systems use an immunochromatographic principle of operation. On a membrane there are two separate immobilised lines of hepatitis B surface antibody (anti-HBs) and anti-human IgG. In both assay systems, the immobilised anti-HBs is closest to the serum application point. Adjacent to the serum application point is a lyophilised conjugate solution (anti-HBs: selenium and anti-HBs: colloidal gold for Determine™ HBsAg and Uni-Gold™ HBsAg assays respectively). If HBsAg is present in the patient serum it will bind initially with the lyophilised conjugated anti-HBs and then secondly with the membrane bound anti-HBs leaving a visible line. As the serum continues to migrate up the membrane, IgG in the patient serum will bind with the membrane immobilised anti-human IgG, forming a second visible line, indicating (a) sample addition and (b) assay validity.

A summary of similarities and differences between the assay systems is presented in Table 1. Both assays were evaluated within their respective expiry dates and testing was performed according to manufacturers instructions. Both assays have the capacity to test whole blood specimens, although this aspect was not inspected during this investigation.

Feature	Determine™ HBsAg	Uni-Gold™ HBsAg
Assay principle	Immunochromatographic	Immunochromatographic
Specimens	Whole blood and serum	Whole blood and serum
Controls (positive / negative) supplied	No	No
Specimen volume (serum)	50µL	60µL
Solid phase	Strip	Membrane in hard cartridge
Buffer flush after serum addition	No	Yes - 75µL
Number and type of immobilised strips	Two: anti-HBs and anti-human IgG	Two: anti-HBs and anti-human IgG
Conjugate type	Lyophilised	Lyophilised
anti-HBs:selenium	anti-HBs:colloidal gold	
Assay time (min)	15	10
Assay evaluation	Visual	Visual

Table 1. Features of two commercial rapid HBsAg assay systems

Axsym™ HBsAg assay

The assay is one of a panel of HBV serological markers that have been customised to operate on the fully automated Axsym™ analyser supplied by Abbott Laboratories.

Briefly, micro-particles coated with anti-HBs are incubated with both patient serum and biotinylated anti-HBs. HBsAg if present in patient serum will form a dual antigen antibody complex, which is then irreversibly bound to a glass fibre matrix. After incubation and wash steps, an anti-biotin: alkaline phosphatase (ALP) conjugate is added. Following a second round of incubation and washing, ALP, if present, will convert the substrate solution to the fluorescent end product of 4-methylumbelliferone. Rate of formation of the end product is measured and is displayed as a sample to negative (S/N) ratio. Ratios are compared to an assay cut-off (CO) and, S/N ratios ≥ 2.0 are qualitatively interpreted as being reactive for HBsAg.

Specificity panel

Fifteen patient sera, previously tested for HBsAg and anti-HBs by Axsym™ assays and methodology comprised the specificity panel. Selection criteria for inclusion were (a) a non-reactive result for HBsAg and (b) a reactive result for anti-HBs. Reactive anti-HBs levels ranged from 10-1000 IU/L. All 15 sera were tested using both rapid HBsAg assays.

Sensitivity panel

Four patient sera, previously tested for HBsAg and anti-HBs by Axsym™ assays and methodology comprised the sensitivity panel. Selection criteria for inclusion were (a) a reactive result for HBsAg with a S/N ratio's of ≥ 250.0 and (b) a negative result for anti-HBs (0.0 IU/L). Each serum was diluted 1:10, 1:50, 1:100, 1:500 and 1:1000 in pooled normal human serum (NHS), previously tested as non-reactive for both HBsAgand anti-HBs (0.0 IU/L) by Axsym™ assays and methodology. The relationship between dilution factor and Axsym™ S/N ratio for all sera are presented in Table 2. Each dilution for all 4 sera was tested using both rapid HBsAg assays.

Serum	Dilution factor (reciprocal)				
	10	50	100	500	1000
1	291.61	155.70	104.85	27.13	15.59
2	435.24	320.69	225.56	75.25	40.71
3	645.59	521.46	488.68	310.34	212.23
4	190.78	63.97	34.36	7.36	4.14

Table 2. Expressed sample to negative ratio's at five dilutions for four HBsAg reactive sera when tested by the Axsym™ HBsAg assay

Linearity of the Axsym™ HBsAg assay was established by first log10 transformation of both the reciprocal of the dilution factor and the resultant S/N ratio. After log transformation, linear regression (LR) analyses were performed. Linearity between the dependent variable (log transformed reciprocal of dilution factor) and independent variable (log transformed S/N ratio) is defined as a correlation coefficient (r) within the range of 0.997 - 1.000.

Results

Rapid assay specificity

All 15 sera of the specificity panel were non-reactive by both rapid methods, giving both methods a specificity of 100%

Rapid assay sensitivity

Comparative assay sensitivity was established by determining the highest dilution for each serum that gave a visible line for HBsAg. Using this rationale, in three (sera 1, 2 and 4) of the four sera, where both assays had a measurable end-point, the Determine™ HBsAg assay had a comparative ten-fold increase in sensitivity over the Uni-Gold™ HBsAg assay (Table 3). For serum number 3, the Uni-Gold™ HBsAg assay had reached its sensitivity limit at a dilution of 1:500. By way of comparison, the Determine™ HBsAg assay was clearly reactive at the final dilution of 1:1000 (Table 3).

	1:10		1:50		1:100		1:500		1:1000	
Serum	[D]	[U]	[D]	[U]	[D]	[U]	[D]	[U]	[D]	[U]
1	++	±	+	-	±	-	-	-	-	-
2	+++	+	++	±	+	-	±	-	-	-
3	+++	+++	+++	++	+++	+	++	±	+	-
4	++	±	+	-	±	-	-	-	-	-

Table 3. Comparative sensitivities of the rapid Determine™ [D] and Uni-Gold™ [U] HBsAg assays when tested against five dilutions of HBsAg reactive sera

Scoring of reactions: +++ Very strong line present. ++ Strong line present. + Line clearly visible. ± Line barely visible. - No antigen line present

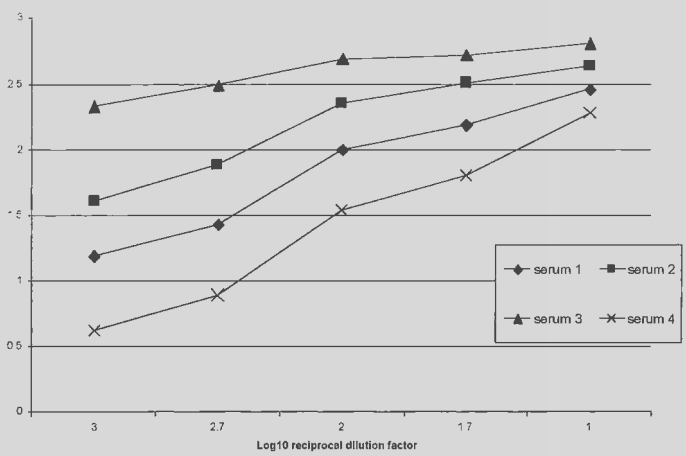
Axsym™ and Determine™ HBsAg assays: relative sensitivities

A comparison of Axsym™ S/N ratios at the sensitivity limit of the Determine™ assay (Tables 2 and 3) demonstrates that the Axsym™ assay has a sensitivity limit approximately fifty times higher than that of the Determine™ assay. To validate this, linearity of the Axsym™ assay was established between the cut-off point (S/N=2.0) and a S/N ratio of 200 [sera 1, 2 and 4] (Figure 1, Table 4). When HBsAg levels exceeded a S/N ratio of 200 a saturation effect is demonstrated [sera 1-3 inclusive] (Figure 1, Table 4).

Serum	1:10 log = [1.0]	1:50 log = [1.7]	1:100 log =[2.0]	1:500 log =[2.7]	1:1000 log = [3.0]
1	S/N = 291.61	S/N = 155.7	S/N = 104.83	S/N = 27.13	S/N = 291.61
	Log = 2.46	Log = 2.19	Log = 2.00	Log = 1.43	Log = 2.46
	*r = -0.986	r = -0.999	r = -0.999	N/A	N/A
2	S/N = 435.24	S/N = 320.69	S/N = 225.56	S/N = 75.25	S/N = 40.71
	Log = 2.64	Log = 2.51	Log = 2.35	Log = 1.88	Log = 1.61
	r = -0.966	r = -0.997	r = -0.998	N/A	N/A
3	S/N = 645.59	S/N = 521.46	S/N = 488.68	S/N = 310.34	S/N = 212.23
	Log = 2.81	Log = 2.72	Log = 2.69	Log = 2.49	Log = 2.33
	r = -0.960	r = -0.978	r = -0.987	N/A	N/A
4	S/N = 190.78	S/N = 63.97	S/N = 34.36	S/N = 7.36	S/N = 4.14
	Log = 2.28	Log = 1.80	Log = 1.54	Log = 0.89	Log = 0.62
	r = -0.997	r = -0.999	r = -0.999	N/A	N/A

r = correlation coefficient

Table 4. Linearity of the Axsym™ HBsAg assay as assessed by LR analysis of log10 transformed reciprocals of dilution factors and S/N ratio's from four HBsAg reactive sera



Discussion

It is a reasonable expectation that technically 'easy-to-use' rapid HBsAg detection methods with similar principles of operation should give similar levels of performance. This study has clearly demonstrated that this is not always the case. We have identified that, although there was no difference in relative assay specificities, considerable differences were noted in relative assay sensitivities, with superior levels being demonstrated by the Determine™ HBsAg assay.

Our results are in line with a large comparative study of rapid HBsAg detection methods conducted by the World Health Organisation (WHO) in May 2001 (4). The WHO study compared the performance of 10 rapid HBsAg methods on (a) a panel of 99 HBsAg positive and 178 HBsAg negative sera (b) five HBsAg seroconversion panels and (c) a panel of 'low-level' (≤ 0.8IU/mL) HBsAg positive sera. Both the Determine™ HBsAg and Uni-Gold™ HBsAg methods had very high associated specificities (99.4% and 100% respectively). However, the Determine™ HBsAg assay was a significantly better performer than the Uni-Gold™ HBsAg assay on the seroconversion panels. Of the five panels, the Uni-Gold™ HBsAg assay failed to be reactive on three of them. The Determine™ HBsAg assay scored at least one reactive result on all five panels. Of the two panels where both rapid assays were reactive, the Determine™ HBsAg assay had a quicker detection rate by eight and five days over the Uni-Gold™ HBsAg assay (4).

A possible contributing reason for the difference in assay sensitivity may be a 'dilution-effect' on serum HBsAg levels that is caused by the buffer flush step immediately following serum addition in the Uni-Gold™ HBsAg assay. A flush step is not used in the Determine™ HBsAg assay. Both assays failed to detect the sample with an HBsAg concentration of 0.8 IU/mL. Our laboratory has previously assessed the limit of detection of the Axsym™ HBsAg assay at 0.1 IU/mL by testing dilutions of a WHO standard preparation (unpublished data). With respect to the fifty-fold increase in sensitivity of the Axsym™ HBsAg method over the Determine™ HBsAg assay together with the linearity of response of the Axsym™ HBsAg method in the S/N range of 2.0 - 200.0, we estimate the limit of detection of the Determine™ HBsAg assay to be in the order of 5.0 IU/mL. This level of detection permits the assay to be used in a diagnostic setting to exclude patients with either acute HBV infections or chronic HBV carriers. In both these clinical settings, HBsAg is present in very high levels.

In summary, in our hands we found that the Determine™ HBsAg assay satisfied all of our diagnostic requirements for a rapid assay as applied in our laboratory as previously stated in the introduction of this article.

References

1. Prince AM. An antigen detected in the blood during the incubation period of serum hepatitis. *Proc Natl Acad Sci USA* 1968; 60: 814-21.

2. Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Hepatitis viruses. In: Schmitt W, Grigg LL, eds. *Medical Microbiology* 4th Edition. Mosby Inc. St. Louis, Missouri. 2002: 591-617.

3. Hollinger FB, Liang TJ. Hepatitis B Virus. In: Knipe DM et al (eds). *Fields Virology* 4th Edition. Lippincott Williams and Wilkins Philadelphia. 2001: 2971-3036.

4. Vercauteren G. Hepatitis B surface antigen assays: Operational characteristics (Phase I). Report 1. *Blood Safety and Clinical Technology, World Health Organisation*. 2001: 1-41.

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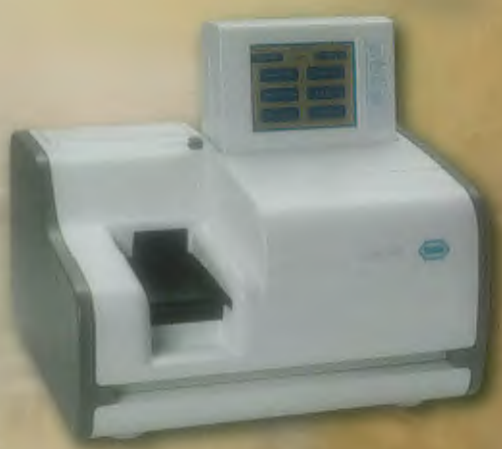

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The Pacific Way

The 25th year of the PPTC started off with a Laboratory Management, Laboratory Information and Quality Systems Course being held from 7 March - 1 April. 13 students attended the course, which was probably the largest number of students that have been at one course since the inception of the PPTC. The Course covered a wide range of topics with the majority of lectures given by the Director of the Centre, John Elliot, with staff members of Wellington Hospital's Laboratory giving talks on their roles and responsibilities in a large New Zealand hospital laboratory. The students also went on tours of Wellington and Kenepuru Hospital Laboratories and the Wellington Blood Centre. They were given masses of lecture notes and handouts to take home to be used for the continuing development of their laboratory's Quality Management Systems.

The students attending came from a variety of medical laboratories, for example Taukea Krypton Okesene Junior from Niue Island is the only full time lab worker in his country, compared with Nurhayati and Ni Ken Ritchie who work at the Jakarta Blood Transfusion Service in Jakarta, Indonesia, serving the large population of Jakarta. Taukeiaho Halauafu from Vaiola Hospital, Nuku'alofa, Tonga was the first student who has gained a NZ Bachelor of Medical Laboratory Science degree, to attend a course at the PPTC.

Gertrude Nteziryayo Arinaitwe would probably have travelled the greatest distance to attend a PPTC course. Gertrude works at the Uganda Blood Transfusion Service in Kampala Uganda. It was interesting to learn of Gertrude's work and the challenges that face her country. Violine Aruafu from the National Referral Hospital in Honiara, Solomon Islands attended the course. She had attended a Clinical Biochemistry Course at the PPTC in 1987 and is now working as a manager in the laboratory. She managed to meet up with her tutor from the 1987 course, Dr Joan Mattingley, and talk about old times.

Three students from Fiji came to Wellington to attend the course. They were from the main hospitals in Fiji, Uraia Rabuatoka from CWM Hospital, Suva, Stella Driu from Lautoka Hospital and Joanna Maravou from Labasa Hospital. They went home enthusiastic to put into practice what they had learned for further development of their labs. It was Toligi Nalu Iese from Princess Margaret Hospital Laboratory, in Funafuiti, Tuvalu third course she had attended at the PPTC. She has only two other fellow workers in her home laboratory so attending courses is important for continuing good laboratory practice.

Our final 3 attendees were Mrs Pham Thi Thanh Huong from the Binh Dinh Department of Health, Mr Nguyen Van Tho from the Biochemistry Department and Dr Vo Dinh Loc from the Haematology Department, Binh Dinh Province Hospital, Vietnam. They were the first students from Vietnam to attend a PPTC course. The PPTC has had an association with the Binh Dinh Provincial Hospital and Bong Son Hospital for several years, and in association with the NZ Vietnam Health Trust, take part in the Pacific Regional Quality Assurance Programme run by the PPTC. Even though English is not their first language, the three Vietnamese students had no problems participating in the various discussions that took place. They have returned to their laboratories enthusiastic to implement Quality Systems.

The Easter break enabled students to visit places outside Wellington. The Indonesian students travelled on a day return to Picton on the Interislander and Lynx ferries. Taukea from Niue spent Easter in Auckland travelling there and back by overnight bus. The three Vietnamese students met up with New Zealand friends who had visited and worked in their hospital back in Vietnam. Nguyen Van Tho visited friends in Raumati Beach, Palmerston North and Blenheim keeping alive the strong bond between NZ and Vietnam Medical Laboratory Scientists.

Participants and tutors from the 2005 Laboratory Management Course.

One evening, after a suggestion from the students, a dinner was held where the students cooked food that is characteristic to their home country. It was all very tasty and the students had no problem sourcing ingredients for their dishes from Wellington shops including frozen octopus from the New World Supermarket in Willis Street. At the conclusion of the course a Certificate Presentation and morning tea was held where Lady Keith, National President of the New Zealand Red Cross spoke to the students and presented certificates to the students. Uraia Rabuatoka from Suva, Fiji replied on behalf of the students and expressed thanks to all who had helped to make the Lab Management Course a great success.

The three Course Participants from Vietnam

This year is the 20th Fiji Medical Laboratory Technologists Association Seminar and will be held between 30 September and 2 October.

Haematology

Special Interest Group

HSIG questionnaire

Journal - *Bloods Reviews* (2005) volume 19, Issue 2, pages 61-68. Disorders of oxidesed haemoglobin.

1. What causes ameamias of oxidesed haemoglobin?
2. What are the three causes of cyanosis in patients affected by this category of anaemia?
3. Iron is usuall transported and stored in its more reactive ferric form whereas ferrous iron participates in oxygen transport systems.

True or False.

4. Explain how minimal methaemoglobin is still formed despite elaborate configuration of ferrous iron in haem and what controls the proportion of circulating methaemoglobin?
5. Describe the cause of a group of disorders known as the Haemoglovin Ms (Hb Ms).
6. Hb Auckland is due to a ..... caused by a ..... of ..... by ..... .
7. Methaemoglobinaemia due to one of the Hb Ms is inherited in an autosomal dominat pattern? True or False.
8. What is the underlying cause of congenital methaemoglobinaemia?
9. Where can the membrane bound form of cytb5r be found and list 3 of its functions?
10. Methaemoglobinaemia due to cytb5r deficiency is inherited as an autosomal diminant disorder?

True or False.

11. Describe the distinguishing features of Type 1 and Type II forms of cytb5r deficiency.
12. What are the three processes thought to be incolced in the production of methaemoglobin in the presence of oxidising drugs?
13. List methods that can be used to identify Hb Ms.

Answers on page 44.

The answers for the HSIG questionnaire in the April 2005 issue were inadvertently omitted. The Editor apologises for this oversight. Below are the answers

Answers to HSIG questionnaire. Journal - Blood Reviews - Volume 17, Number 4, December 2003, Pages 209-213

1. Congenital neutropenia is defined as an abnormality present at birth and is usually, but not necessarily, of genetic cause.

2. Neutropenia (neonatal allo-immune neutropenia:NAIN, primary auto-immune neutropenia-AIN), recurrent bacterial infections

3. Monosomy 7, activating mutations in the oncogene ras, G-CSFR mutation

4. Periodic neutropenia inter-spaced with normal or near normal neutrophil counts, recurrent fever, mouth ulcers and an excess of typical childhood upper respiratory tract and ear infections, peri-anal cellulitis (in severe cases)

5. False

6. False

7. Exocrine pancreatic dysfunction, neutropenia (often intermittent), skeletal abnormalities, bacterial infections, severe eczematous-like skin condition, short stature, metaphyseal dysostosis, epiphyseal dysplasia, liver function abnormalities, renal tubular defects & psychomotor retardation

8. Glucose-6-phosphate translocase enzyme

9. True

10. Activating mutations in the Wiskott Aldrich syndrome protein (WASp), myelokathexix, Pearson's syndrome, Barth syndrome

11. True

12. Barth syndrome

13. Refractory sideroblastic anaemia, exocrine pancreatic failure

New Zealand Journal of
Medical
Laboratory
Science

60 Years of Continuous Publication Journal Prize

In 2006 the Journal will celebrate 60 years of continuous publication. To celebrate this memorable occasion, the NZIMLS will award a special prize, worth $500, for the best case study accepted and published in the Journal during 2006.

Case studies bring together laboratory results with the patient's medical condition. Many such studies are presented by our professional members at conferences and SIG meetings, yet rarely are submitted to the Journal. Start thinking and planning now to submit your interesting case study to the Journal. Not only may you win this special prize, but definitely will earn you CPD points. As all articles in the Journal are peer-reviewed, start thinking about submitting during the latter half of 2005. Please feel free to contact the Editor, Deputy Editor or Members of the Editorial Board if you want advise or guidance.

You must be a financial member of the Institute (Fellows, Members and Associate Members) during 2006 to be eligible. No formal application is necessary. All case studies published during 2006 (April, August and November issues) will be considered. The Editor, Deputy Editor and the President of the NZIMLS will judge the published case studies in December 2006. Their decision will be final and no correspondence will be entered into.

Med-Bio Journal Award

med·bio

Med-Bio offers an award for the best article in each issue of the New Zealand Journal of Medical Laboratory Science. All financial members of the NZIMLS are eligible. The article can be an Original, Review or Technical Article, a Case Study or a Scientific Letter. Excluded are Editorials, Reports, or Fellowship Treatises. No application is necessary. The Editor and Deputy Editor will decide which article in each issue is deemed worthy of the award. If in their opinion no article is worthy, then no award will be made. Their decision is final and no correspondence will be entered into.

Winner of the April 2005 issue was Jenny Bennett from the Enteric Reference Laboratory, ESR, Porirua for her article "Vibrio cholerae in New Zealand. N Z J Med Lab Sci 1995; 59 (1): 3-5.

NZAP

New Zealand Association of Phlebotomists, SIG of the NZIMLS
Aiming for Excellence

Checking patient details

The single most important duty performed in Patient Services is the correct and appropriate checking of patient details prior to collecting the specimen. Obtaining a specimen from the wrong patient can have serious and even fatal consequences. Misidentification of a patient may result in disciplinary action and subsequently dismissal.

At a minimum the laboratory requires at least two forms of patient identification, which must match on both the request form and the specimen:

- Patient name, NHI or code and date of birth.

However in the controlled circumstances of collection rooms, rest homes, hospitals and with home visits, all relevant patient demographics shall be checked by collection technicians/phlebotomists.

Greeting and Aadressing a patient

Patients will judge you and your ability by the manner in which you greet them. Many people are nervous about having a test performed, and it is part of your role to put them at ease. A **smile** and an acknowledgement are vital in achieving this.

The technician will call the client in the waiting area to a collection room by asking for: e.g. Mr John Brown, Mrs Eleanor Smith, etc. It is important to use the first name as well as the surname to avoid an incident when "same names" may be in the waiting area, a relatively common occurrence and "same name" stickers shall be used on the requisition form highlighting this. It is appropriate to use Mr, Mrs or Ms when addressing clients and where possible, proving ourselves to be polite, professional and not overly familiar.

Checking details

When a client is seated in the privacy of the clinical area, **ask** the patient to state their **full name, address** and **date of birth,** and clarify the spelling with them if necessary, e.g. Smith or Smyth, correct any abbreviations e.g. Kate or Katherine or Kathryn. Do not raise your voice or ask loudly. Ask them in a sensitive manner -

"could you please tell me your name?"

or

"may I check the spelling of your name?"

"can you tell me your address please?"

"would you please tell me your date of birth?"

or, showing the person the request form (particularly useful for ESL people) ask then to confirm

"could you please confirm that your name, address and date of birth (pointing to each in turn) are correct?"tive manneritten on the formtification, which must match on both the request form and the requisit

Ensure that what the patient verbalises matches the details on the form. The safest and therefore the **most** appropriate way of checking patient details is to **ask** their address, **ask** their date of birth, and **ask** their address. By asking for information there can be no possibility of miss identification, as the client is giving the collection technician the information, enabling correction to the requisition form as necessary.

Ask any additional questions related to the tests at this time, such as:

"could you please tell me the time of your last dose?"

and

"when did you pass this sample?

Once the collection process has been completed it is 'good practice' for the technician to show the patient the samples, asking them to confirm by checking and signing the requisition form, that the samples are indeed theirs and that they have been labelled correctly.

Regular patients

You may think you remember the names and faces of all your regular patients, however, the highest incidence of misidentification is with regular patients. You must check their name, address and date of birth.

Coded patients

Do not ask for name, date of birth and address from patients presenting with a coded request form. Show them the form and ask them for confirmation that it is theirs.

Rest home patients or confused patients, patients with an intellectual disability

In a rest home situation, ask a senior staff member from the rest home to escort you to the patient and touch them on the shoulder, to check the patient's wristband with you if one is present or to perform an I.D. with the patient's records. Never assume who the correct resident is. Elderly people can often be confused and will answer "yes" to any question asked of them.

In the case of patients with intellectual disabilities, the same identification process as described above can be performed with the care giver or guardian. In either event ask the identifying person to sign the requisition form and print their name indicating they have completed the correct identification process on behalf of the patient.

Hospital patients

The information recorded on the patient's wrist band must correspond exactly with the information on the sample and the request form. The collection technician must check these details completely. In the event that the patient is unconscious or too ill to answer the identification questions, the collection technician must seek the assistance of the patient's primary nurse/caregiver to complete the identification process as described above for confused patients. ian must check these details completely. In the event that the patient is unconscious or too ill to an

Patients from out of town or overseas

If a patient is attending a clinic from another town/city/country ensure that their local contact address and telephone number is noted on the requisition form and/or their own Doctor's address and telephone/fax number if results are to be forwarded directly there.

Trainees, assessors and tutors

If you intend to have another person present with you at the time of collection, it is most important to introduce them to the patient, to explain who they are and why they are there, and to ask permission

for them to remain whilst the procedure is carried out. The patient has an absolute right to decline and must be made to feel comfortable about doing so.

Privacy

Do not invade patient privacy by asking for personal information in front of other patients. The patients name, address and fasting status may be asked at reception, as it cannot be linked to clinical information. All other patient particulars must be asked in privacy.

When seeking clarification of tests by phone or when assisting a patient to contact their practitioner to ask for information or to have an extra or different test performed etc, do not use a reception phone. Any such request or clarification must be done in private.

Do not attempt to explain tests to a patient. You may be misunderstood, and or quoted out of context, or the practitioner may have chosen for clinical reasons to perform a test that the patient may not be aware of. Beware of being drawn into conversations of a medical or personal nature where your comments could be misinterpreted.

Do not become involved in discussions with patients about the particular merits of any health professional or institution, and never recommend a particular practitioner to a patient.

Treat patients, health professionals and other staff as you would wish to be treated.

Nicki Killner
Medlab South Limited

Corrections

A few mistakes occurred in the NZAP section of the November 2004 journal issue. The item **"A manager's perspective"** was attributed to Trish Watt. It should be attributed to Lorna Gribble from Waikato Hospital. Diana Bell, who contributed the item **"Reflections of a QPT'** is from Waikato Hospital as is Gaye Duffill, who contributed the item **"Exam nerves from the over 40's"**.

Rob Siebers, Editor

Answers to HSIG questionnaire

1. Inappropriate oxidation of the ferrous iron found in the haem group of haemoglobin, results in a dysfunctional molecule incapable of oxygen exchange under physiological conditions. This leads to anaemias known as anaemias of oxidised harmoglobin.
(i) the presence of haemoglobin M; (ii) methaemoglobin redustase deficiency; or (iii) toxin-induced production of methaemoglobin.

2. False.

3. Some oxidation of Fe2+ to Fe3+ does occur. This is due to the intermittent discharge of oxygen as a superoxide ion (O-2) leaving the haem iron in the Fe3+ state. Methaemoglobin reductases in the red cells ensure that the proportion of methaemoglobin does not exceed 1%, above which will result in anaemias of oxidised haemoglobin.

4. Globin chains aid in stabilising the haem-oxygen complex through the formation of the haem pocket. An amino acid substitution will result in the structure alteration of the haem pocket which leads to spontaneous oxidation of the Fe2+ ion embedded in haem. Such variants give rise to haemoglobin Ms.

5. Mutation, substitution, His87, Asn.

6. True.

7. It is caused by a deficiency of reduced nicotinamide adenine dinucleotide (NADH)-cytochrome b5 reductase (cytb5r).

8. Membrane bound form of cytb5r can be found in the endoplasmic reticulum and mitochondrial membrane in red cells. Cyb5r participates in desaturation and elongation of fatty acids, biosynthesis of cholesterol and P-450-mediated drug metabolism.

9. False.

10. Type 1 - only involves deficiency of red cell soluble form of the enzyme. Type II - involves both the soluble and membrane bound forms of cytb5r. Cyanosis is also accompanied by severe mental retardation and neurological impairment.
(i) Direct oxidation of the haem iron, Fe2+ to Fe3+, a process that needs oxygenated haemoglobin, and is important in nitrite-induced production of methaemoglobinaemia, and (iii) a drug or chemical, such as the amino- and nitro-benzenes, may be metabolised to a derivative which is capable of initiating methaemoglobin formation.

11. Hb Ms can be identified by electrophoresis and pH 7.1, differential UB spectrometry, mass spectrometry, and DNA sequencing.

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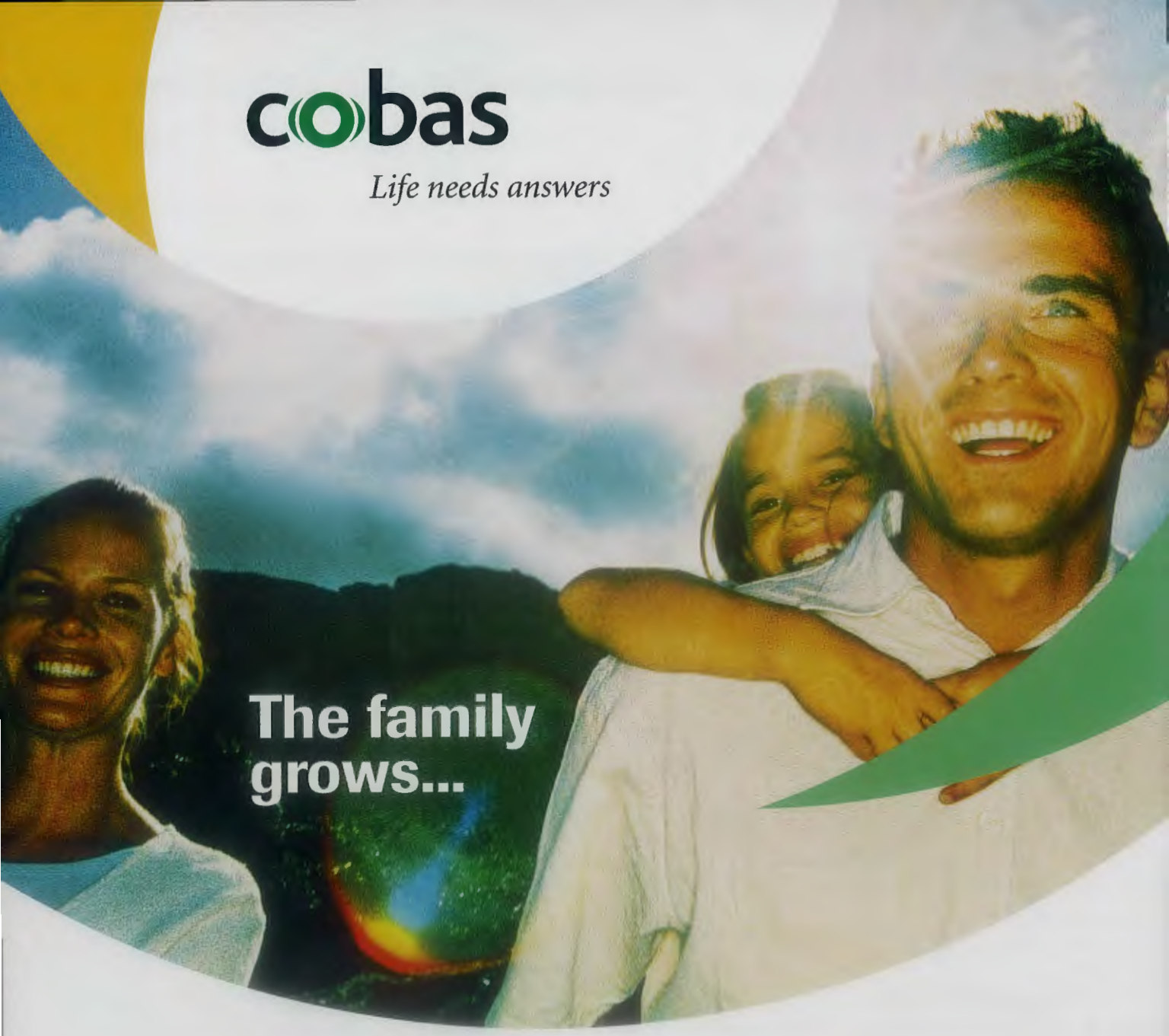

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