

A history of blood glucose meters and their role in self-monitoring of diabetes mellitus

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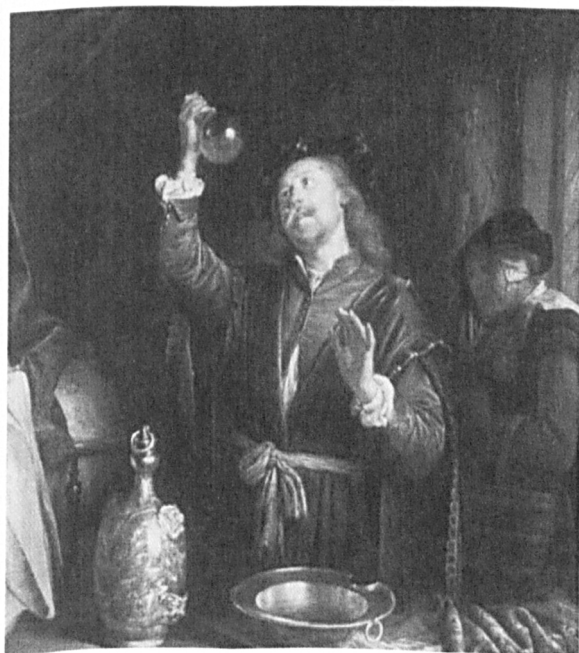
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Introduction

It is over 40 years since Anton Clemens at the Ames Research Division, Miles Laboratories, in Elkhart, Indiana, USA, developed the first blood glucose meter. It combined dry chemistry test strips (Dextrostix) with reflectance photometry to measure blood glucose. The concept of dry chemistry would be elegantly developed later for the analysis of other analytes.¹ Consequently, the first blood glucose meters represent an important landmark technology, which influenced the extensive growth of point-of-care (POC) testing in the mid-1980s.² Great progress has been achieved in the development of blood glucose meters and this continues to be an active field of study and research.^{3,4}

The passage of time has also led to a greater understanding of the management and treatment of diabetes mellitus. Major studies have recommended the need to maintain near-normal blood glucose concentrations



A physician looking at a container of urine, using his senses of sight, touch, hearing, smell and taste to make a diagnosis.
See this image in colour at www.bjbs-online.org

ABSTRACT

Self-monitoring blood glucose (SMBG) systems have the potential to play an important role in the management of diabetes and in the reduction of risk of serious secondary clinical complications. This review describes the transition from simple urine sugar screening tests to sophisticated meter and reagent strip systems to monitor blood glucose. Significant developments in design and technology over the past four decades are described since the first meter was introduced in 1970. Factors that have influenced this evolution and the challenges to improve analytical performance are discussed. Current issues in the role of SMBG from the clinical, patient and manufacturer perspectives, notably adherence, costs and regulations, are also considered.

KEY WORDS: Blood glucose.
Blood glucose self-monitoring.
Diabetes mellitus.

and to measure glycated haemoglobin (HbA1c) every four months to reduce the occurrence and severity of serious secondary clinical conditions, most notably microvascular, macrovascular and neuropathic complications.⁵ The benefits of closer monitoring of blood glucose have also been shown to apply to some patients with type 2 diabetes.⁶ The range of laboratory tests available to monitor both types of diabetes has been critically reviewed.⁷

The first part of this review describes the early history of diabetes monitoring, dominated by urine tests, and explores their link to the origin and evolution of blood glucose meters. The second part presents selected examples of blood glucose meters, which illustrate the innovation and diversity in design, technology, functions and performance of a device now available worldwide to benefit people with diabetes.

It should be noted that the dates in which specific blood glucose meters were introduced varied between Europe and the USA. Variation also applies to the units of glucose measurement used, and, for simplicity and comparison purposes, blood glucose concentrations in the text are reported in international units (mmol/L) and the conversion factor used to mg/dL is 18.

Urinary glucose measurement

The Egyptians made the first mention of diabetes around 1500 BC. The Greek physician Aretaeus (130–200 CE) noted a disease with symptoms of constant thirst, excessive urination and loss of weight, and named the condition 'diabetes', meaning 'flowing through'. The first clear

reference to diabetes was made by an Arab physician, Avicenna (980–1037 CE), who accurately described in detail the clinical features and complications of the disease and its progress.

During mediaeval times an attempt was made to identify various diseases by examining urine samples for appearance, colour, sediment and often taste. It was not until the early 19th century that glucose was identified as the sugar present. This association was supported in 1838 when George Rees, a physician at Guy's Hospital in London isolated sugar in excess from the blood serum of a diabetic patient.⁸

It was also possible to detect excess sugar in the urine and various chemical tests were developed, although there was still no treatment for diabetes, except with diet. Trommer, in 1841, and Von Fehling, in 1848, devised urine qualitative tests using the reducing properties of glucose with alkaline cupric sulphate reagents to produce coloured cuprous oxide.⁹ Jules Maumene was first to develop a very simple reagent 'strip' in 1850, in which drops of urine were added to strips of sheep's wool containing stannous chloride, which gave a black product if sugar was present. George Oliver, the English physician and physiologist, published *Bedside Urine Testing* in 1883 and marketed a range of reagent papers for testing urine, and used the reduction of alkaline indigo-carmin to detect sugar.¹⁰

Towards the end of the 19th century a quantitative blood

sugar method was published which used copper reduction and gravimetric measurement.¹¹ Stanley Benedict devised an improved copper reagent for urine sugar in 1908,¹² and this became, with modifications, the mainstay of urine monitoring of diabetes for over 50 years.

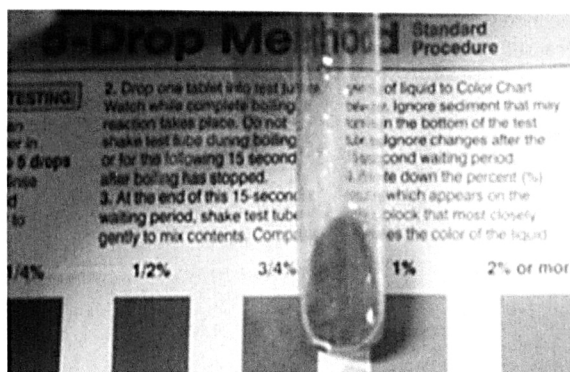
Leading specialists in diabetes, notably Elliott Joslin in the USA, advocated a self-management concept relating to diet, exercise and frequent urine testing in an attempt to keep the urine sugar-free.¹³ In 1913, Frederick Allen, a leading US diabetologist, identified a clinical need to develop an accurate method for the quantitation of blood sugar for diagnostic purposes.¹⁴ In the first two decades of the 20th century Bang, Folin, Lewis, Benedict, Shaffer and many others pioneered laboratory methods for quantitative blood sugar. Proteins were removed and the reduction of cupric salts, ferricyanide or picrate used with titrimetric or, more often, colorimetric endpoints.^{15–17} Despite continual improvements in reducing sample volume, improving colour stability and precision, manual blood sugar estimations in the laboratory were limited and mainly confined to diagnosis and critical care management, rather than for monitoring purposes.^{18,19}

A breakthrough in the treatment and improvement in the lives of diabetics came about in 1921 when Frederick G. Banting, his assistant, Charles Best, and J. R. Macleod succeeded in the identification of insulin, the pancreatic hormone deficient in diabetes, which was confirmed in

Table 1. Summary of potential sources of variation and error.

| Source of error | Blood glucose result error |
|---|------------------------------------|
| Pre-analytical | |
| Incomplete deposition of reagents on test strip | ↓ ↑ |
| Test, calibration, control strip surface damaged | ↓ ↑ |
| Test strip exposure to high temperature during storage | ↑ |
| Test strip is date expired | ↓ ↑ |
| Testing at high altitude | ↑ – glucose oxidase |
| Operator | |
| Diet or medication containing excessive galactose | ↑ – GDH-PQQ |
| Diet or medication containing, maltose or xylose | ↑ – GDH-PQQ |
| Diet containing excessive ascorbic acid (vitamin C) | ↓ or ↑ – GDH biosensor only |
| Acetaminophen (paracetamol) | ↓ – glucose oxidase biosensor |
| L-Dopa | ↓ or ↑ – glucose oxidase biosensor |
| High haematocrit | ↓ |
| Low haematocrit | ↑ |
| High blood triglycerides | ↓ – Glucose oxidase |
| Low blood oxygen | ↑ – Glucose oxidase |
| High blood uric acid | ↓ – Glucose oxidase |
| Analytical errors | |
| Miscoding test, calibration, control strip to meter | ↑ or ↓ |
| Contamination to sampling site (e.g., with fruit juice) | ↑ |
| Insufficient blood applied to test zone | ↓ |
| Reagent strip not fully inserted into meter | ↓ |
| Overloaded test strip | ↑ |
| Post-analytical | |
| Misreading of result display | ↑ or ↓ |

GDH: glucose dehydrogenase, PQQ: pyrroloquinoline quinone. *Varies according to blood glucose monitoring system.



Clinitest was introduced by Ames in 1945, and utilised a copper reagent tablet that contained all the reagents required for a urine glucose test. See these images in colour at www.bjbs-online.org

human studies. Large-scale commercial extraction and purification of animal insulin led the way to the treatment for diabetes and to the development of improved testing systems.

Urinary dry-reagent testing

Self-testing of urine using Benedict's copper reagent required heat for colour development, which presented practical difficulties. This was neatly resolved with the introduction of Clinitest by Compton and Treener at Ames in 1945, with a modified copper reagent tablet containing all the reagents required (i.e., sodium hydroxide, citric acid, sodium carbonate and cupric sulphate).²⁰ The tablet was added to a small quantity of urine in a tube, which reacted rapidly to generate sufficient heat to cause the mixture to boil. Glucose present in the urine was oxidised, and the blue cupric sulphate reduced, causing a change in colour from blue to green to yellow to orange. Semiquantitative results were obtained by visually comparing the colour formed with a colour chart provided. A similar concept of reagents in tablet form was used to develop a test for measuring ketones in urine in 1950.²¹

A major achievement in clinical chemistry has been the development of dry-reagent chemistry. The first ever dry-reagent test strip developed in the 19th century was the litmus paper.²¹⁻²³ The development of a dry-reagent test strip for urinary glucose measurements heralded a new era in the monitoring of diabetes by the use of the key enzyme glucose oxidase, first identified by Muller in 1928 and characterised by Keilin and Hartree in 1948. In 1956, Keston and Teller independently used glucose oxidase in linked reactions to measure glucose. This was later adapted to measure plasma glucose in the clinical chemistry laboratory by manual or more often automated methods.^{24,25}

Continued research at the Miles-Ames Laboratory was destined to be a key element in the history of blood glucose meters. The quest for a more convenient and specific method culminated in a 'dip and read' urine reagent strip, Clinistix, in 1957.²⁶ Initially, Clinistix used stiff filter paper impregnated with glucose oxidase (GO), peroxidase and orthotolidine. In a coupled reaction, glucose oxidase catalysed the oxidation of glucose to gluconic acid and, in the presence of oxygen, formed hydrogen peroxide, which is catalysed by peroxidase for the oxidation of orthotolidine to a deep blue chromogen.

It was well recognised then that urine testing had a number of significant limitations for diabetic monitoring. Fluid intake and urine concentration affect test results according to the sensitivity of the reagent strip, and urine glucose can only be retrospective of the current glycaemic status. Positive results only occur when the renal threshold for glucose is exceeded and this may vary in longstanding diabetes or pregnancy; more significantly, negative results do not distinguish between hypoglycaemia, euglycaemia and even mild hyperglycaemia.⁷ The correlation between urine and plasma glucose has been shown to be inconsistent.²⁷ Consequently, blood became the preferred sample, most easily collected by fingertip capillary puncture, which reflects 'real time' blood glucose concentrations.

Blood glucose dry-reagent test strips

In 1957, Kohn showed that Clinistix could also give approximate results for blood glucose.²⁸ In 1965 an Ames research team under Ernie Adams went on to develop the first blood glucose test strip, the Dextrostix, a paper reagent strip which used the glucose oxidase/peroxidase reaction but with an outer semipermeable membrane which trapped red blood cells but allowed soluble glucose to pass through to react with the dry reagents.²⁹ A large drop of blood (approximately 50–100 μ L) was applied to the reagent pad, and after one minute the surface blood was gently washed away and the pad colour visually assessed against a colour chart to give a semiquantitative blood glucose value. However, the colours were difficult to visualise as the colour blocks were affected by ambient lighting conditions, and variation in individual visual acuity made it difficult to obtain accurate and precise readings. Although the Dextrostix was designed for use in doctors' offices, the concept of diabetic patients undertaking the measurements had not been considered.

Around the same time, the German company Boehringer Mannheim developed a competitive blood glucose strip, the Chemstrip bG. This was easier to use because the drop of blood was wiped off using a cotton wool ball, and, as it had a dual colour pad (one beige, the other blue), it was easier to visualise the colour.

The visually monitored blood glucose test strips, Dextrostix (Ames) and Chemstrip bG (Boehringer Mannheim), were widely used in clinics, surgeries and hospital wards, notably intensive care units, for adults and

neonates. However, colours were prone to fade and it was realised that there were highly significant visual variations in the assessment of colours across the range of glucose concentrations using Dextrostix.²⁹ These limitations became the trigger to develop an automatic, electronic glucose test strip reader to improve precision and give more quantitative blood glucose results.

A 'bright' start – the first blood glucose meters: 1970–1980

Interest in diabetes was intensified during the 1970s by the introduction of glycated haemoglobin (HbA1c) measurement as an index of the quality of glycaemic control, and a major trial of type 2 diabetes commenced in 1977 in the UK to study the effect of close control of blood glucose and the risk of clinical complications.⁶ The concept of self-monitoring of blood glucose (SMBG) using reflectance meter systems gained gradual support through published evaluations and international conferences, notably that held in 1978 in New York.³⁰ However, many reports identified potential practical problems and emphasised the need to improve portability, ease of use, accuracy and precision that could be achieved by patient home-monitoring and to be able to act on the result to adjust their therapy. There were also concerns about the funding of meters,³¹ and liability in the event of errors.

Anton Clemens at Ames developed an instrument to produce quantitative blood glucose results with Dextrostix in the late 1960s, and the first model became available in 1970.³² He applied the key principle of using reflected light from the surface of the solid strip, which was captured by a photoelectric cell to produce a signal that was displayed by a moving pointer on three analogue scales, equivalent to 0–4, 4–10 and 10–55 mmol/L blood glucose. The Ames Reflectance Meter (ARM) weighed 1.2 kg, mainly due to its casing and lead acid rechargeable batteries. A standard reference strip was used for calibration. According to a few small studies, good correlation with a laboratory reference method was obtained and the device was stated to be reliable and gave rapid results.^{33,34} However, the sample application, wash and blot technique to remove the red blood cells, and timing were all critical to precision.³⁵ Consistently higher results were found in the low range,³⁶ with low results in the higher ranges compared to laboratory methods. The meter cost around \$495 and was only available for a doctor's office and hospital emergency departments. The first reported patient to use blood glucose meter was Dick Bernstein, who suffered from type 1 diabetes and had episodes of hypoglycaemia resulting in hospitalisation.³²

In 1972 the Japanese company Kyoto-Daiichi (later Arkray) produced the Eytone blood glucose meter and had a marketing agreement with Ames to launch the product in the USA. The Eytone also used reflectance photometry and the Dextrostix reagent test strips. It had an AC adaptor to use mains power and a single analogue scale and two standard strips for calibration. As it used mains power, it was lighter and easier to operate than the ARM, and, more importantly, it was slightly cheaper. Generally, performance from a limited number of studies was considered acceptable, with good precision and correlation.^{37,38} A much later study stressed the need for caution in its use in monitoring and

therapy of neonatal hypoglycaemia due to poor precision.³⁹ All these studies emphasised the importance of operator training, continuing practice and repeated calibration for accurate and precise results.

In 1974, Boehringer Mannheim produced the Reflomat, a reflectance meter using a modified reagent strip, requiring a much smaller volume of blood (20–30 μ L), which was removed more simply by wiping with a cotton wool ball. Up to now, the blood glucose meters available were designed for testing in doctors' offices and it was not until the mid-1970s that the idea of diabetics self-testing was contemplated. Assessment of performance showed close agreement with laboratory reference methods,⁴⁰ with some evidence that it was suitable for self-monitoring of blood glucose in type 1 diabetes and could lead to improved control.⁴¹ Similar findings were reported from a small study group of diabetics during pregnancy.⁴²

The Dextrometer, launched in 1980, was the first meter with a digital display and could be operated by battery or mains power. The meter was calibrated using Dextrostix loaded with a synthetic whole blood standard of 7.2 mmol/L,⁴³ but was never introduced into the UK or Republic of Ireland. Instead, the Ames Glucometer, developed by Kyoto Daiichi, became available in the UK and was thought to be a 'superior meter' due to its smaller, more compact size, with fewer operator-dependent steps. Eventually it became available in the USA, replacing the Dextrometer. Good correlation and precision were reported,⁴⁴ and it was suggested that the Dextrometer was suitable for home monitoring.⁴⁵

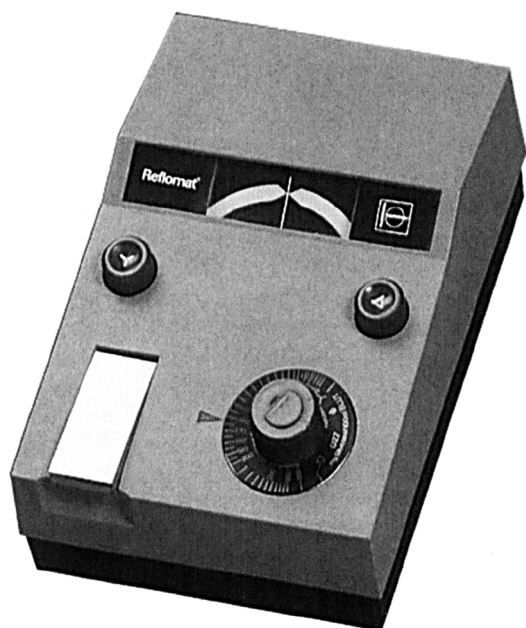
Glucochek, the first of a series of blood glucose meters produced by Lifescan, became available in 1980 in the UK. The instrument, later known as Glucoscan, was a battery-driven, digital reflectance meter manufactured by Medistron in England, with the reagent strip produced in Japan by Eiken.⁴⁶ Early models had a number of technical problems, notably the short life of the rechargeable batteries and an inaccurate timer which led to poor precision and correlation.⁴⁷

The pioneering work of Anton Clemens had set the stage for further developments to improve blood glucose meter systems. Other companies joined Ames and Boehringer Mannheim, leading to diversification in appearance, technology and performance.

Meeting the challenge: 1981–1990

The 1980s was an active phase in the evolution of meters, which were becoming easier to use, smaller in size, with more variation in design, often with software memory to store and retrieve results. Reagent strips were also changing to accept smaller volumes of blood, and some were barcoded for autocalibration and quality assurance. Most significantly, towards the end of this decade, the first enzyme electrode strips were introduced, providing a choice of instrument (i.e., using either reflectance or electrochemical principles) to measure blood glucose.

In 1981, Ames introduced the Glucometer I, a lightweight, portable, battery-operated, digital reflectance meter with a 'countdown' timer with audio signals. The instrument still used Dextrostix and had stored calibration with alarm signals for high results (>22 mmol/L) and low battery



Boehringer Mannheim introduced the Reflomat in 1974 and the Reflux in 1984. See these images in colour at www.bjbs-online.org

charge. Laboratory evaluations showed good precision and excellent correlation to a hexokinase-based glucose method, and it was recommended for bedside monitoring of blood glucose.⁴⁸ In a comparison study with two other meters, the Glucometer I gave the best correlation over a wide range of glucose concentrations (1.7–22 mmol/L).⁴⁹ In 1986, Ames developed an improved two-pad reagent strip, Glucostix, which was used with the Glucometer II and which possessed additional features, such as push-button programming for a preset calibration, and in a laboratory evaluation gave good correlation and precision and was found easy to use.⁵⁰ In the same year, Ames introduced a data management system, Glucofacts, which could be linked with Glucometer M to store over 300 results with date and time, and also with Glucometer GX, a smaller meter available in 1990.

Lifescan introduced Glucoscan II and Glucoscan 2000 in 1983 and 1986, respectively, with improved meter reliability. However, assessments of the ease of use and analytical performance by laboratory and nursing staff using Glucoscan 2000 were generally inconsistent and disappointing.^{50–52} The aptly named OneTouch meter was introduced in 1987 and was regarded as a 'second generation' blood glucose monitoring system (BGMS) because it utilised a modified sampling procedure. A small volume of blood was applied to the reagent strip that was already inserted in the meter, and timing began automatically, with results displayed after 45 seconds. The strip required no washing, wiping or blotting, and reduced operator variation. Few performance evaluations were published but a small Canadian study showed that 30% of results had unacceptable deviations from the laboratory method.⁵³

In 1982, Boehringer Mannheim (BM) launched Reflocheck, a small portable reflectance meter using Reflotest strips which were wiped with a cotton ball and had a barcode for calibration. Evaluations showed excellent correlation and good precision,⁵⁴ and results from a diabetes screening study in general practice demonstrated cost benefits.⁵⁵ In 1984, BM marketed the first of a series of Accu-

Chek (Reflux in Europe) meters, which used improved reagent strips that required smaller volumes of blood, including BM Test-Glycémie 20-800R that could also be read visually with a more stable colour. In 1986, Accu-Chek II became available and received good performance reports in comparison with other equivalent BGMS.⁵⁶

Biosensor blood glucose meters

The development in the 1950s of the oxygen electrode by Clarke for the measurement of pO_2 was the forerunner in the development of the first biosensor electrode. The first description of a biosensor, an amperometric enzyme method for glucose measurement, was made by Clarke and Lyons in 1962.⁵⁷ This concept was incorporated in the measurement of blood glucose in the Yellow Spring 24AM 'desktop' analyser, which became commercially available in the mid-1970s.

The first blood glucose biosensor system, the ExacTech, was launched in 1987 by MediSense. It used an enzyme electrode strip developed in the UK at Cranford and Oxford universities. The strip contained glucose oxidase and an electron transfer mediator, ferrocene, which replaced oxygen in the original glucose oxidase reaction; the reduced mediator was reoxidised at the electrode to generate a current detected by an amperometric sensor.⁵⁸ The meter was available in two highly original forms, a slim pen or a thin card the size of a credit card. Evaluation reports showed that accuracy, precision and error grid analysis were satisfactory.⁵⁹ The use of electrode technology thus heralded what became designated the third-generation BGMS.

In 1987, with the increased use of SMBG systems, the American Diabetic Association (ADA) lowered the preferred glucose meter deviation compared to laboratory reference methods to 15%.⁶⁰ A useful evaluation statistical tool, error grid analysis, was developed by Clarke *et al.*⁶¹ and applied by Kochinsky *et al.*,⁶² which gave an improved measure of accuracy related to clinical significance and decision-making.

Emergence of smaller meters: 1991–2000

Glucose became one of the most frequently measured analytes in clinical units, primary care and by patients for monitoring at home, made possible through the availability of systems based on dry-reagent test strips with visually read end-points and/or simple-to-use reflectance meters and biosensors. However, the first-generation blood glucose systems had a number of operator-dependent steps, with the possibility of obtaining misleading results adversely affecting patient treatment. These were highlighted in a number of publications at the time and led to the Department of Health issuing a Hazard Notice.⁶⁵ These difficulties were mainly in obtaining a sufficient volume of blood, inaccuracies in timing the application and removal of blood from the test strip, inaccurate wiping technique, calibration/coding errors, lack of maintenance and quality control procedures. In light of these concerns, many manufacturers went on to develop systems that eliminated or minimised these operator-dependent steps.

Improvements in blood glucose monitoring systems

The number of smaller, handheld BGMS continued to increase and Bayer, Abbott and Roche purchased pioneer companies Ames, MediSense and Boehringer Mannheim, respectively, between 1995 and 1998. Both major diabetes studies, the UKPDS and the Diabetes Control and Complication Trial (DCCT)⁶⁶ were completed and blood glucose monitoring was regarded as an integral part of intensive diabetic treatment and management. In 1996 the ADA lowered the target variation to 5% between meters and the laboratory method.⁶⁴ This proved to be a very exacting challenge across the full range of blood glucose concentrations for manufacturers. A recent review highlighted many inherent limitations and technical difficulties in analytical and clinical accuracy for whole blood glucose using meters.⁶⁵ The need to produce blood glucose systems that were safe to operate by patients became a high priority in the design and functions available and in minimising possible sources of error interference (Table 1, see page 84).

There was continued concern about accuracy and precision in the 'hypoglycaemic' range and in 1994 a campaign, 4's the Floor (4 mmol/L), raised the importance of self awareness and the clinical risks of hypoglycaemia. Other issues included using more effective evaluation and the importance of patient education, compliance rates and costs. Many comprehensive BGMS evaluations were performed by the Medical Devices Agency.^{66,67}

Ames (Bayer) continued its glucometer series with Glucometer Elite (1993), adapted from Glucocard previously marketed by ArkRay in 1991. This was a small, compact meter that used electrode sensor technology and required just 5 μ L capillary blood and utilised 'capillary fill' uptake of blood, thus eliminating strip wiping and blotting. The Glucometer Esprit (1997) was also a biosensor instrument, and offered a 100-test memory that could be downloaded to a personal computer via the Bayer WinGlucofacts data management system. Boehringer Mannheim released Reflolux S (1991), a reflectance meter that used the BM 1-44 Glycaemie strips, requiring 20 μ L blood, but needed wiping



With the 21st century came a number of different electrochemical glucose meter systems, including the OneTouch Ultra (top right) from Johnson & Johnson. See this image in colour at www.bjbs-online.org

and gave results after 120 seconds. Evaluation gave excellent correlation with the hexokinase laboratory method and results were clinically accurate in the low (<4 mmol/L) and high (>10 mmol/L) ranges.⁶⁸

A major advance came with the introduction of the Lifescan (Johnson & Johnson) OneTouch II in 1992, a reflectance blood glucose system that eliminated the need to time accurately the application of blood to the test strip and its removal prior to the measurement of the colour. The system was simple to operate, precalibrated and a result could be obtained in approximately 45 seconds. It was more reliable and accurate than its predecessor and had a storage capability of 250 results. It was used in a study to assess the value of 'memory' meters and the results indicated improved patient motivation and glycaemic control.⁶⁹ OneTouch II performed most accurately in a comparison of four meters at low blood glucose concentration (<4 mmol/L) but nevertheless failed to meet the ADA criteria.⁷⁰

Boehringer Mannheim launched the Accutrend range of meters in 1992, using a non-wipe technique for the measurement of glucose (e.g., Accutrend Mini [1994] and Accutrend Alpha [1996]). The use of barcoded reagent test strips also prevented the misuse of those from a different lot code. The meters were precalibrated to give whole blood equivalent results, were simpler to use and only required 20 μ L blood.

Critically ill patients on oxygen therapy or with impaired oxygen transport may give discrepant glucose results with systems using glucose oxidase methodology by either over-estimation (low pO_2) or under-estimation (high pO_2). In 1991, HemoCue (Angelholm, Sweden) introduced the HemoCue B system, a dual-wavelength (660 and 840 nm) photometer that was battery or mains powered and intended for hospital and primary care use.⁷¹ HemoCue was the first capillary fill, non-wipe system, employing a special disposable microcuvette containing dried reagents, which acted as a blood collection tube and a measuring cuvette. The reagents utilised the enzyme glucose dehydrogenase (GDH), coenzyme, diaphorase and a tetrazolium salt. The addition of a 5- μ L capillary blood sample initiated a coupled reaction with glucose to form a coloured formazan, the amount of which was proportional to the glucose

concentration. Results were available in approximately 20–240 seconds, depending on glucose concentration. Although the system was very simple to use as the blood sample was drawn into the cuvette by capillary action, the reagent microcuvettes had to be stored in a refrigerator and brought to room temperature before analysis.

Due to the advantages of biosensors, many manufacturers, including Roche (Boehringer Mannheim), started to develop biosensor systems. In 1996, Roche released its first biosensor blood glucose meter, the AccuChek Advantage, which utilised GDH and the coenzyme pyrroloquinoline quinone (PQQ). Although more sensitive than the glucose oxidase reaction, it was prone to interference by high concentrations of maltose or galactose.⁴⁵ Other electrochemical meters were produced by MediSense (Abbott). The models included the MediSense Companion II (1994) and the Medisense Precision QID (1998).

Continuous glucose monitoring systems

Continuous glucose monitoring systems (CGMS) give greater insight into the direction, magnitude, duration, frequency and possible causes of glucose fluctuations in response to meals, insulin injections, hypoglycaemic episodes and exercise throughout the day. Compared to conventional blood glucose measurements performed four to six times a day, results are provided every 10 minutes for up to 72 hours. However, a blood glucose meter is still required by users, as a conventional fingerprick sample is needed several times a day to calibrate the system. The CGMS systems work by inserting a small catheter containing the sensor subcutaneously. The sensor measures the glucose in the interstitial fluid and results are transmitted to a monitor for storage or immediate display.

An alternative mode of monitoring blood glucose became available with the Glucowatch Biographer (1999; Cygnus, California, USA). This device, worn as a 'wristwatch', uses reverse iontophoresis to stimulate the secretion of subcutaneous fluid, and glucose content was measured using an electrode/GO/biosensor unit. The process allowed automatic, frequent monitoring with alarms for designated low and high results. In a comparison with two existing blood glucose meters, there was good correlation and results were clinically accurate both in the clinic and home setting.⁷²

Blood glucose monitoring systems: 40 years on

Most of the progress in the development of blood glucose meters has centred on data management and the trend towards the connectivity of information technology systems, especially for glucose systems for the hospital market. In addition, greater consideration has been given to the special needs of persons with diabetes in the design of meters, operation and data management. Examples of adapted design features include rubber grips for easier handling and enlarged display screens that may be backlit for clarity. Meters have become easier to use with minimal operating steps, autocalibration, sample underfill detection, coloured sampling ports, and haematocrit correction. More advanced data handling in tabular and graphical forms with

calculation of 7-, 14-, 30- and 90-day averages also became available. Results could be downloaded to personal computers, games consoles, iPhones or managed via specialised software. In 2003, manufacturers were given a performance quality standard, ISO 15197. This specified that 95% of results should be within ± 0.83 mmol/L of the reference glucose method for concentrations < 4.2 mmol/L, and within 20% for higher concentrations.⁷³

Bayer rebranded its glucometers as Ascensia for a series that used both glucose oxidase or GDH catalysed reactions. The Ascensia Breeze (2003) used autodiscs rather than strips, and a 2–3 μ L sample with autocalibration. Ascensia Breeze II (2007) required just 1 μ L of sample with a rapid response and a more advanced data management system. One of the most popular Bayer meters, the Ascensia Contour, was launched in 2004 using GDH-flavin adenine dinucleotide (FAD) chemistry with capillary fill test strips, which only required 0.6 μ L of sample. Offering results in 15 seconds, it was plasma calibrated with a wide linear working range of 0.6–33.3 mmol/L. Evaluation results for the Contour met ISO 15197 accuracy criteria and was found to be suitable for patient self-monitoring.⁷⁴ Other meters included the Contour Didget (2009) that could be connected to a games console (Nintendo DS) to encourage consistent testing by supervised children with type 1 diabetes. The Contour USB (2010) had a plug-and-play facility to connect to Glucofacts Deluxe software for enhanced display features (e.g., error messages, low or high results and results related to meal times).

Johnson and Johnson (Lifescan) produced at least five variations of the popular electrochemical OneTouch glucose meter system, commencing with the OneTouch Ultra in 2001. This used Ultra reagent strips (glucose oxidase), a 1 μ L blood sample and was one of the earliest meters to be plasma calibrated. In one study, the system was shown to be precise, meeting ISO 15197, and 99% of results were clinically accurate.⁷⁵ The Ultra has been used in alternative site testing, such as the forearm or hand, which is intended to reduce sampling pain and so improve patient compliance of glucose monitoring.⁷⁶ The OneTouch UltraSmart collects and organises test results as an electronic 'logbook', and in a randomised, controlled trial (2004) its use was shown to be associated with a reduction in HbA1c as compared to meters that used paper records.⁷⁷ OneTouch Ultravue (2009) had a colour display, a reagent strip ejector for used strips, and a simple interface without push buttons; features that can help the less-able diabetic. The UltraVue met established accuracy and precision performance criteria in an evaluation study.⁷⁸

The MediSense SoftSense blood glucose meter (2002) was the first meter launched in the UK to offer a fully automated sensor using an integral lancing device and electrode capable of collecting a sample and performing glucose measurements on a blood sample obtained from the forearm, upper arm or the base of the thumb. Owing to the provision of two separate ports for the sensor electrode, the system offered a back-up facility allowing blood glucose measurements to be performed from a fingerprick capillary blood sample in the usual manner. The fully automated system obtained a blood sample by applying a vacuum to the skin and lancing it. The blood was then automatically transferred to a test electrode and the glucose measurement initiated.

Table 2. Summary of developments in the evolution of blood glucose systems for self-monitoring.

| Year | Development | Example | Company |
|------|---|------------------------|---------------------|
| 1957 | First reagent strip using glucose oxidase reaction | Clinistix | Ames |
| 1964 | Modified reagent strip for blood glucose | Dextrostix | Ames |
| 1970 | Reflectance photometry with Dextrostix | Ames Reflectance Meter | Ames |
| 1973 | Mains-powered, single analogue scale | Eyestone | Ames |
| 1974 | Reduced blood volume, strip wiping | Reflomat | Boehringer Mannheim |
| 1980 | Digital display, whole blood standard | Dextrometer | Ames |
| 1980 | Automatic timing | Glucochek/Glucoscan | Lifescan |
| 1981 | Improved countdown timer with audio alarm | Glucometer I | Ames |
| 1981 | Stored calibration, low/high result alarms | Glucometer I | Ames |
| 1986 | Data storage of results | Glucometer M | Ames |
| 1987 | Non-wipe, automatic timing, 45-second measurement time test strip | OneTouch | Lifescan |
| 1987 | First biosensor enzyme electrode sensors | Exactech | Medisense |
| 1991 | Capillary-fill sampling with 5 μ L blood | HemoCue | |
| 1997 | Downloading results to personal computers | Glucometer Esprit | Bayer |
| 2001 | Plasma calibration | OneTouch Ultra | Johnson & Johnson |
| 2002 | Catering for visually impaired persons | AccuChek Voicemate | Roche |
| 2003 | Biosensor using coulometry, alternative site testing | Freestyle Freedom | Abbott |
| 2003 | Autodisc of 10 strips replaced reagent strips | Ascensia Breeze | Bayer |
| 2005 | 17-test strip barrel | AccuCheck Compact | Roche |
| 2008 | Talking blood glucose meter | SensoCard Plus | BBI |

In 2003, Therasense launched the Freestyle, one of the smallest meters then available (just 38 g), which used GDH-PQQ and coulometry. The GDH-PQQ is coated on the working electrode of the test strip and all the sample glucose is used to generate a total charge or area under the current time curve for a coulometric analysis of glucose. The coded test strips were precalibrated for plasma-equivalent results, and with a 0.3 μ L sample volume it was suitable for alternative site testing. Coulometric strips are characterised by their robust performance, low sample volume (0.3 μ L) and are claimed to be less susceptible to variable temperature, haematocrit and high concentrations of paracetamol, uric acid and vitamin C.^{79,80}

The Precision Xceed and Optium Xceed test strips used GDH-NAD to improve specificity and the meters could also be used with β -ketone strips for the analysis of blood ketones during illness or in the event of hyperglycaemia, and were reported to be more sensitive and clinically useful compared to urine ketone screening.⁸¹ Since the introduction of those first meter systems from Bayer, Roche, Abbott and Lifescan, many more manufacturers/distributors are coming to the market, creating more competition. Nova Biomedical, an established biosensor specialist, developed StatStrip systems in 2007, which used multiwell electrode technology to reduce interference by haematocrit and non-glucose-reactive substances. Another new development, by Home Diagnostics (UK), has been the introduction of disposable blood glucose meters, TRUEOne and TRUEOne Twist, with meter and test strips combined (the strip canister lid forms the meter), which are provided as a single item on prescription. In addition, a 'talking' blood glucose meter is now available from BBI, the SensoCard Plus, for visually impaired patients with diabetes.

Table 2 summarises significant developments in the evolution of blood glucose monitoring systems from 1957 to 2010.

Overview

It is evident that great progress has been made during the past 40 years and, although there are slight variations, the modern blood glucose meter has evolved into an almost standard size and shape. These are battery powered, handheld, easy to use and contain advanced micro-electronics and software to perform a range of useful functions. Reagent strips have not changed in appearance for many years but now only require 0.3–1 μ L blood, and electrode biosensor strips dominate the market. Lancets are now designed to be less painful, with safer means of use and disposal. Many blood glucose systems are readily available and the Diabetes UK website currently lists over 26 glucose systems.

Discussion

There are a number of issues relating to the effective use of SMBG, including the evidence for monitoring type 2 diabetes, patient adherence, financial implications, and the standardisation and regulation of BGMS.

Diabetes is a most important healthcare challenge and it was estimated that in the UK the prevalence of diabetes in 2010 was 4.3% (2.8 million) with a dramatic and alarming two-fold increase compared to data for 1996.⁸² Type 1 diabetes is insulin-dependent and accounts for about 10% of

diabetes, with most commonly an early age of onset (<40 years). So, 90% are type 2 cases with typically a later age of development, although it is becoming more common in young persons with 'lifestyle obesity', and may be treated by diet, glucose-lowering agents or require insulin. These statistics are highly relevant to SMBG for all those involved in diabetes management.

There is wide agreement that frequent daily blood glucose measurements are highly appropriate in type 1 and type 2 diabetics on insulin.^{69,83,84} However, there is conflicting evidence on the clinical benefits of SMBG for the large group of non-insulin-treated type 2 patients.⁸⁵ Positive benefits include reduced morbidity and less hospital admission,^{82,86} while negative outcomes include no significant improvement in glycaemic control as measured by HbA1c,⁸⁷ or even, it has been suggested, a small increase in clinical depression.⁸⁸ The consensus appears to be that daily SMBG in type 2 diabetes is appropriate for those on insulin, or during intercurrent illness, and those prone to hypoglycaemia. It should be noted that some type 2 diabetics on oral treatment also require glucose monitoring, but less frequently. Target blood glucose concentration limits prior to meals and two hours post-prandial have been defined and are similar both for type 1 and type 2 diabetics.^{83,89}

Adherence to the guidelines for the use of SMBG is difficult to assess. In a large multinational study, patients reported adherence rates for SMBG of 70% and 64%, while diabetes healthcare providers' estimates were only 44% and 24% for type 1 and type 2 diabetes, respectively.⁹⁰ These lower rates are generally in line with other smaller studies.⁹¹

A number of barriers to optimal adherence to SMBG have been identified and include demographic factors, notably in ethnic minority groups, and significantly psychosocial elements such as anxiety, self-perception of diabetes and vulnerability to complications, and the quality of support available by the healthcare provider and family.⁹² Patients may be stressed by the responsibility of self-care and the demands of regular and possibly repeated painful fingerprick, or lack the motivation and discipline required. Younger patients may be more comfortable with new technology, data handling and the need to maintain the meter. Research has placed a consistent emphasis on an individual-focused approach of management to improve motivation by education and positive support in order for the patient to make informed decisions of their status and treatment using SMBG.⁹² It is important to realise that SMBG is just one of the integrated components of diabetes care, along with a healthy diet, exercise and, significantly, lifestyle.

The cost of blood glucose meters and reagent strips varies considerably between suppliers (meters often may be given away free of charge, or typically cost £12–£20). However, the most significant expenditure in SMBG is for the reagent strips (approximate cost: 18–28 pence each), and this may have serious financial implications for the patient and NHS prescriptions. An effective balanced cost analysis of SMBG is required to include education, training and support, but also the potential cost-savings of a reduction in the many and varied complications of diabetes, which require additional care and treatment, and may seriously affect the quality of life.

Manufacturers of BGMS are faced with a number of pressures to maintain commercial viability and to conform to a variety of performance accuracy criteria against no single standard,^{65,93} with ISO 15197 most commonly used as the

yardstick for analytical performance. The Medicines and Healthcare products Regulatory Agency (MHRA) monitors the safety, quality and performance of blood glucose meters, test strips, lancing devices and lancets, and notification of sources of adverse incidents may be made by the manufacturer, healthcare professionals or patients. However, it is disappointing to note that significant errors continue to be reported as medical device alerts, and include incorrect result displays and the need to withdraw meters or reagent strip lots, or the issue of additional and sufficient advice for safe use, by some of the leading companies. Other significant issues are the appearance of parallel imports and 'fake' strips, which emphasise the need to educate and train patients to use monitoring systems competently and make meaningful use of their results. It has been suggested that there is a trend towards reduced investment in the development of new meter/strip technology.⁸⁶ However, in view of the failed attempts to develop alternative, notably non-invasive or minimally invasive glucose monitors, BGMS remain the only recommended practical device for SMBG in adults.⁸⁴

In conclusion, with the advances made in BGMS technology, blood glucose monitoring is readily available for a vast number of patients with diabetes. Any existing barriers to the training and education of patients, adherence and costs will need to be addressed urgently. With an increasing prevalence of diabetes worldwide, there is little doubt that blood glucose meter/strip systems used effectively will continue to be an essential component of diabetic self-care. □

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