Self-monitoring of Blood Glucose
Historical perspective
Monitoring Glycaemic Control: Early History

Methodology: Urinalysis for glucose

In 1941 Clinitest® effervescent urine sugar testing tablets launched by Bayer (formerly Miles Laboratories)

Uses alkaline copper sulphate and Na citrate – forms colour in re-hydrated state dependent on glucose content – ‘non-specific’ test subject to interference
Monitoring Glycaemic Control: Early History

Methodology: Urinalysis for glucose

In 1954 Glucotest/Testape roll licensed by Eli Lilly to Boehringer Mannheim.

During 1960s the ‘dipstix’: Diastix, Clinistix, Chemstrip uG available.

- In 1964 Combur-Test (BM) for glucose, protein and pH of urine.
- Later range extended to include ketones – Ketostix/Ketodiastix.
Monitoring Glycaemic Control: Early History

Methodology: Urinalysis for glucose

Positive features:
Painless and ‘LOW COST’

Limitations:
Inconvenient – double voiding
Regarded as “dirty” unhygienic
Results difficult to understand
Not reflective blood glucose- 
Fails to detect hypoglycaemia
Interfering substances
Concept of ‘normal’ renal threshold false

![Histogram showing renal threshold for glucose variations](image)

- **n = 47**
- **mean = 7.8±1.8 mmol/L**

Insulin dependent diabetics. Variations in renal threshold for glucose varies between 3 and 12 mmol/L. *Walford, 1980 SMBG Symposium, UK*
Early History: Self-Monitoring Blood Glucose (SMBG)

Visual Reading: ‘semi-quantitative’ estimations


1st dry-reagent blood sugar test-strip using immobilised glucose oxidase with horse-radish peroxidase and a colour indicator. Modifications: covering over enzymes and dye with water resistant material on a plastic support

Limitations:
- Large drop of blood required to cover test zone (30μl)
- Reaction time 60 seconds
- Remove blood - wash/blot or wipe
- Read result within 1-2 seconds after washing
- Reliance on colour matching

Glucose oxidase
Glucose + O₂ → gluconic acid + H₂O₂

Peroxidase
H₂O₂ + dye* reduced → oxidised dye + H₂O colourless

*chromogen
Early History: Self-Monitoring Blood Glucose (SMBG)

Quantitative estimation: Reflectance Meters (ARM)
(i) photometric (colourimetric) – ‘Desk-Top’

1970 Ames Reflectance Meter (ARM)
    inventor Anton (Tom) H Clemens,
    battery powered, bulky, expensive
1972 became the Eyetone Meter (Kyoto Daiichi, Kagaku Co Japan)
    used AC plug-in adapter, less expensive
Reagent test strips - Dextrostix

1974 Reflomat (Stat Tek) Reflectance Meter
    launched by Boehringer Mannheim,
Reagent test strips - Reflotest

Requirement:
    precisely calibrated meters
### Early History: Self-Monitoring Blood Glucose (SMBG)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956</td>
<td>Priscilla White, <em>Diabetes</em> 1956;5: 55</td>
<td>“Do you think patients should learn how to... <em>Suggestions considered laughable</em>”</td>
</tr>
<tr>
<td>1970s</td>
<td>SMBG related manuscripts (Sönksen and Walford)</td>
<td>Rejected by British Diabetes Association - <em>hostile response</em></td>
</tr>
<tr>
<td>1970s</td>
<td>Richard Bernstein failed repeatedly to publish his own experience using SMBG to prevent ‘hypos’ &amp; improve control</td>
<td></td>
</tr>
</tbody>
</table>
| 1975 | St Thomas Hospital, London, introduced SMBG to a pregnant person with history of ‘hypos’ and a lowered renal threshold. | Admitted to hospital 3rd trimester  
  “Why can’t I do this at home?”  
  Taught to use Eyetone reflectance meter and self-manage treatment, able to normalised blood glucose  
  Delivered a healthy, normal weight baby  
  Regarded by colleagues as “*A dangerous practice...*” |
Early History: Self-Monitoring Blood Glucose (SMBG)

Automated Evaluation: Reflectance Meters (ARM) (i) photometric (colourimetric) – ‘Desk-Top’

1968 Haemo-Glukotest developed (improved 1979). Remains the gold standard of accuracy for purely visual blood glucose determination.

Reflectance Meters

Bulky
Heavy
Expensive

1979 Dextrometer

1974 Reflomat (Stat Tek) Meter

1st film-based colourimetric test-strip
<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Journal &amp; Volume</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Keen and Knight</td>
<td>Lancet 1962;1:1037</td>
<td>Self-sampling of BG (‘blotting” paper method) dispatched to hospital laboratory</td>
</tr>
<tr>
<td>1964</td>
<td>Rennie et al</td>
<td>Lancet 1964;2:884</td>
<td>Validation of a rapid enzyme ‘test strip’- Dextrostix</td>
</tr>
</tbody>
</table>
Early History: Self-Monitoring Blood Glucose (SMBG)

Key Symposia during 1980s:

1980 Workshop on Home Monitoring of Blood Glucose
Tattersall et al. Nottingham, UK

1980 Symposium on Home blood glucose monitoring
Diabetes Care; 3:57-186

1982 Symposium on potentially implantable glucose sensors
Diabetes Care; 5:147-283
Early History: Self-Monitoring Blood Glucose (SMBG)

Automated Evaluation: Digital Read-out meters
(1) photometric test strips LifeScan (J&J)

1981 Glucockek / Glucoscan: developed by Medistron (UK)
acquired by Johnson & Johnson in 1986

‘First Generation’ Meters:
Systems had considerable user influence on the results
and a narrow haematocrit range
Test times remained relatively long from 40 seconds to 2 minutes
### Early History: Self-Monitoring Blood Glucose (SMBG)

Automated Evaluation: Glucose meters - digital read-out
(1) photometric test strips – **Bayer (ex Miles)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Device</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td><strong>Dextrometer</strong></td>
<td>Digital version of Dextrostix meter</td>
</tr>
<tr>
<td>1985</td>
<td><strong>Glucometer II</strong></td>
<td>From Bayer with memory capability</td>
</tr>
<tr>
<td>1986</td>
<td><strong>Glucometer M</strong></td>
<td>With event marker and computer interface</td>
</tr>
<tr>
<td>1987</td>
<td><strong>Glucofacts™</strong></td>
<td>Data management System</td>
</tr>
</tbody>
</table>
Early History: Self-Monitoring Blood Glucose (SMBG)

Automated Evaluation: Glucose meters - digital read-out

(1) photometric test strips –Roche (ex Boehringer M)

1983  Reflofux / Accu-check: from Roche diagnostix
1986  Reflolux II / Accu-check II
1987  Reflolux II M / Accu-check II M, memory & PC interface
1990  Reflolux S / Accu-check III
Early History: Self-Monitoring Blood Glucose (SMBG)

Second Generation Meters - requirements
1. Recognise blood sample application and time the reaction,
2. Eliminate need for blood removal step by separation of plasma from RBCs, or correct for blood colour in colorimetric devices or use electrochemical reactions
4. Incorporate checks to identify defects and user error in procedure

1987 One Touch meter: introduced by LifeScan
Automated digital read-out meter using photometric test strips

Simplify: No timing, wiping, blotting or washing of blood
Blood Glucose Testing: Test-strip Technology

(2) Electrochemical test strips – Abbott (ex MediSence)

1987-88 ExacTech

“..first proper portable glucose sensor”
a non-wipe system, using capillary filling

Second Generation meter
Developed by Genetics International in conjunction with Cranfield and Oxford Universities. Company re-named Travenol and then MediSence

Ferrocene based ‘Mediated’ sensor*

Glucose
Glucono lactone

Gox (ox.)
Gox (red)
Mediator (red)
Mediator (ox.)
Electrode

2e–

Gox = glucose oxidase

*Disposable ‘Screen-printed’ sensor design
Blood Glucose Monitoring: Evolving Technology

**Second Generation Products** – *technologies to*

- Simplify test procedure:
  - recognise blood sample application and time reaction
- Eliminate need for blood removal step (separate plasma from RBC or correction for blood colour in colorimetric devices or by use of electrochemical reactions)
- Incorporate software and other checks to identify defects and user error in procedure

- More accurate results with less user influence

LifeScan One Touch, Wampole Answer, Bayer Encore, Roche Accu-Chek Easy, Abbott ExacTech,
Blood Glucose Monitoring: Second Generation

Over the next 15 years – *further developments*

- Developing capillary methods for blood sampling
- Addressing $pO_2$ effects in electrochemical sensors with change to GDH enzyme
- Improving haematocrit range with new reaction matrices
- Improving dynamic range
- Improving the error detection routines
- Decreasing the test time down to 5 seconds
- Decreasing the sample volume required to $1 \mu l$ or less
Blood Glucose Monitoring: Second Generation

‘Capillary’ filling introduced between plastic layers

1994 Bayer Glucometer Elite Diabetes Care System
1997 Bayer Dex device

Filter layers:
Accu-Chek Easy

Hydrophilic meshes:
Roche Accu-Chek Advantage,
MediSence Precision QID Companion 2 products

Hydrophilic polymer foam:
LifeScan SureStep

Minimize spillage/contamination, movement on the electrodes during test and ensure adequate sampling
## BG Test-strip Technology: Enzyme/mediator Systems

<table>
<thead>
<tr>
<th>Enzyme Co-enz</th>
<th>Mediator</th>
<th>Indicator</th>
<th>Product examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOD</td>
<td>FAD Air oxygen/$\text{H}_2\text{O}_2$</td>
<td>Leuco dye</td>
<td>Chemstrip bG, One Touch</td>
</tr>
<tr>
<td>GDH-PQQ</td>
<td>Gold</td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tbody>
</table>

**Glucose oxidase:** specific for glucose but susceptible to $p\text{O}_2$ effect

**GDH-PQQ:** eliminates oxygen effect but is less specific, but also detects maltose and galactose

**HK-G6PDH:** eliminates oxygen effect but is more sensitive to heat and humidity

**Mediators** (‘electron transfer molecules’): Key Breakthrough

Help to minimize interference especially when using low potential mediators, improved with a third electrodes

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Indicator</th>
<th>Product examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenylendiamine</td>
<td>molybdic</td>
<td>Compact and Go</td>
</tr>
<tr>
<td>NAD Phenanthroline quinone</td>
<td>Electrode</td>
<td>Precision Xtra (A)</td>
</tr>
</tbody>
</table>

‘Trade-offs’ when selecting enzymes/co-enzymes and mediators to optimise performance, reliability and cost
Selection of Self-Monitoring Blood Glucose Devices 2008

Volume of sample (microL)
Results Time (seconds)

Coding required:
Yes 22 (71%)

Alternate Site Testing:
Yes 27 (87%)

Altitude (feet):
>7000    (4)
10,000   (13)
10,000-11,000  (14)

Calibration:
plasma all (31)
plasma + whole blood (1)

Operating Temperature
40-122 (°F)

Haematocrit Range (%)
0-70

‘An on-going process’
Developments: ‘trade-offs’ all systems have limitations
Blood Glucose Monitoring: Lancets

Less painful, alternative site testing, more convenient, integrated ‘sensor-sampling’ systems
on-going developments
Third Generation: Continuous Glucose Monitoring

Sensors & Transmitters

Medtronic MiniMed Guardian/Paradigm RT
Abbott Navigator
DexCom

DexCom G2
DexCom G3
CGMS - 722
Navigator
Blood Glucose Monitoring: Continuing Evolution

Glucose Sensors

- Intermittent 'spot' monitoring
  - Finger and alternative site glucose meters

Continuous Glucose Monitoring (CGM)

- Invasive
  - Intravenous
    - sc sensors
  - Microdialysis
- Minimally invasive
  - Reverse iontophoresis
  - Micropore/Microneedle

Non-invasive

- Transdermal
  - Reverse iontophoresis
  - Sonophoresis
  - Skin suction blister technique
  - Impedance spectroscopy

- Optical
  - Spectroscopy:
    - NIR, MIR, Raman
    - Photo-acoustic
    - Scattering/occlusion
    - Fluorescence
    - Thermal Infrared
    - Polarimetry
    - OCTomography
    - Kromoscopy
Evolution of Blood Glucose Monitoring: Summary

Pre-1950s: Qualitative Urinalysis: solutions/tablets

1950s: Dry chemistry test-strips urine glucose, protein, pH

1960s: Blood glucose strips visual reading – semi-quantitative

1970s: First Generation - Reflectance Meters (Qualitative)

1980 - Second Generation – no timing or blood removal refinements – capillary filling, smaller blood volume (less pain, alternate site testing), shorter test time, better accuracy/precision, less interference, integration miniaturisation (portability), connectivity, no coding etc

2000: Third Generation – Biosensors for Continuous Glucose Monitoring (CGM)

? Fourth Generation – Non-invasive monitoring

“An on-going evolution towards complete patient independence”
Blood Glucose Monitoring: Fourth Generation

Thank you for your attention
## Blood Glucose Products: Performance Parameters

<table>
<thead>
<tr>
<th></th>
<th>Accu-Chek Aviva</th>
<th>Compact Plus</th>
<th>One-Touch Ultra 2</th>
<th>Bayer Contour</th>
<th>LifeScan Lite/FreeStyle Freedom</th>
<th>Precision Xtra</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range mg/dl</strong></td>
<td>10-600</td>
<td>20-600</td>
<td>10-600</td>
<td>20-500</td>
<td>20-500</td>
<td>20-500</td>
</tr>
<tr>
<td><strong>Haematocrit %</strong></td>
<td>20-70</td>
<td>25-65</td>
<td>30-55</td>
<td>0-70</td>
<td>15-65</td>
<td>30-60</td>
</tr>
<tr>
<td><strong>Humidity %</strong></td>
<td>10-90</td>
<td>20-85</td>
<td>10-90</td>
<td>10-90</td>
<td>5-90</td>
<td>10-90</td>
</tr>
<tr>
<td><strong>Temperature °F</strong></td>
<td>43-111</td>
<td>50-104</td>
<td>43-111</td>
<td>41-113</td>
<td>40-104</td>
<td>50-122</td>
</tr>
<tr>
<td><strong>Altitude (feet)</strong></td>
<td>&lt;10,150</td>
<td>&lt;10,000</td>
<td>?</td>
<td>&lt;10,000</td>
<td>&lt;7,200</td>
<td></td>
</tr>
<tr>
<td><strong>Underdose protection</strong></td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Double dosing</strong></td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
There’s Progress for you

Thank you for your attention