Feature Article

The Small-Size Electrode Type Blood Glucose Meter "Antsense III" and Point of Care Testing

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Antsense III is a light, compact and portable electrode type blood glucose meter which is capable of measuring the blood glucose concentration with only a small drop of whole blood sample, so simply and quickly. It also ensures reliable measurements in in-situ diagnosis with its advantage of less susceptibility to variations of oxygen partial pressure and hematocrit value, which largely depend on temporal conditions of patients. The above achievements are generated by our ingenious ideas such as the cartridge type blood cell separating membrane with enzyme electrode method, which integrates hydrogen peroxide electrode with glucose oxidase immobilized membrane, and the refreshing mechanism of the hydrogen peroxide electrode and the glucose oxidase immobilized membrane.

Introduction

HORIBA has expanded its activity in the medical diagnostic field by marketing the Point of Care Testing (POCT) devices, Pentra 60 series and LT/LC series, which provide blood test results in in-situ treatment and diagnosis. In October 2000, entrusted with the production by Sankyo Co., Ltd., we newly added in our lineup the small-size electrode type blood glucose meter Antsense III, the smallest meter among the HORIBA's medical equipments. The meter is capable of measuring the blood glucose concentration with only a small drop of whole blood sample, so simply and quickly. Approximately 7,000 units have been in the market mainly for physicians and nursing staffs. Hereunder we introduce the features and advantages of Antsense III, which has just been improved independently by HORIBA, reflecting the market requirements to the former models.

Demands for Blood Glucose Concentration (Blood Sugar Level) Measurement

As generally known, elevated blood sugar level brings higher risk of vascular disorder and cardiac disease, whereas low blood sugar level results in serious cases such as losing consciousness. If the blood sugar level is out of normal control as diabetes, the level should be monitored quickly and accurately in any time. For this purpose, the demand for a portable and accurate blood glucose meter has increased more than ever. Antsense II, the former model, enables diagnosis with in-situ measurement of exact blood sugar level, and instruction of treatment for low/high blood sugar conditions. It is also used to continuously monitor and control the blood sugar level to stabilize patient's condition during surgical operation or dialysis.

Blood sugar level rises/falls depending on physical conditions and the normal level is within 70 to 140 mg/dL. A typical rising factor is that the splanchnic nerve controlling liver, the storage of glucose, is stimulated (due to mental stress). As a falling factor, the insulin activity is well known. Insulin is one of hormones formed by pancreas. When it acts on a cell, glucose contained in blood is taken into the cell, and the glucose is consumed to produce energy for vital activity. Blood sugar level can stay elevated (i.e. diabetes) if the following conditions occur and remain; insulin production is low due to a genetic factor or virus infection; insulin does not act normally on its target cell due to a genetic factor; or if too much calorie intake or obesity rises blood glucose amount far more than that taken into cells by insulin activity, and result in poor glucose consumption. The constantly elevated blood sugar level causes peripheral vascular and nerve diseases, results in complications (such as cardiac disease, cerebral stroke, loss of sight, renal failure, and neuropathy), then lowers the quality of life (QOL).

The number of diabetic patients is estimated as 150,000,000 in the world. In Japan, 7,400,000 people are strongly suspected, and if potential patients are added, the total number is assumed as 16,200,000 (approximately 12% of Japanese population). Diabetic patients treated in hospitals in Japan are assumed as 2,200,000 only, and many people are not aware of their developing diabetes and complications, or are consciously staying untreated. The demands of tests for diabetes will largely increase in future.

General Description of Antsense III

Appearance and Operation

Antsense III (Figure 1) is light, compact and portable as shown in Table 1. It features the power-on start, and ensures safe and easy measurement as cartridge type. The operating procedure is as follows:

1. Collect a venous blood sample with an injector.
2. Put a drop of the blood sample on the blood cell separating membrane as the sample dropping area, and press the start switch.

Then the result appears on the display.

Figure 1 Antsense III

*1: The storage liquid in this tank intakes waste reactants through the sensor surface and simultaneously keeps the surface in optimum moist condition required for enzyme reaction.

Table 1 Specifications

Dimensions	20 cm (W)× 18 cm (D)× 6.5 cm (H)
Mass	800 g (excluding the AC adapter)
Measuring range	10 to 1,000 mg/dL
Memory	Covers 100 times of measurement
Printer	Built-in type (with sticky paper)
External output	RS-232C

Satisfied Users' Requirements

Antsense III satisfies the following users' requirements posed to the conventional models:

- Wider measuring range with the lowest concentration of 10 mg/dL
  The measurement accuracy is improved with the most frequent sample amount from 10 mg/dL to 250 mg/DL.
- Built-in printer saves handwriting works of the measurement results.
  Printed on sticky paper which is repeatedly affixed and removed, the result is easily attached on a chart.
- RS-232C external output (standard specification)
  Applicable to on-line system and electronic medical charts.

Measurement System

The measurement system is based on the enzyme electrode method, which integrates hydrogen peroxide electrode with glucose oxidase immobilized membrane.

With the sensor structure (Figure 2), the glucose concentration is measured after dropping of the blood sample and detection of electric current induced by the reactions as follows.

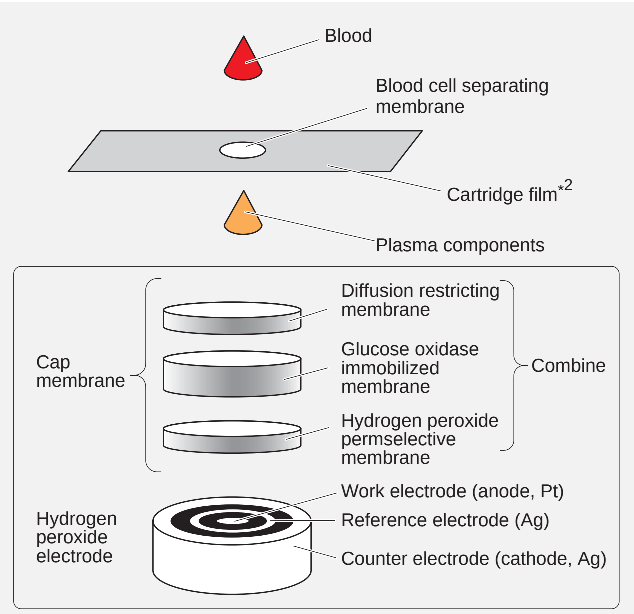

Figure 2 Sensor Structure

*2: Polyethylene film to support the blood cell separating membrane

1) Plasma components are separated from the whole blood sample with the blood cell separating membrane.
2) Glucose contained in plasma penetrates the cap membrane on which glucose oxidase is immobilized.
3) When penetrating the cap membrane, the glucose is decomposed to gluconic acid and hydrogen peroxide by catalysis of glucose oxidase.

Reaction formula

Glucose + $H_2O \rightarrow H_2O_2$ + Gluconic acid

Glucose oxidase (GOD)

4) Hydrogen peroxide is decomposed on the surface of electrode to generate electric current.

$$\text{Anode} \quad : 2H_2O_2 \rightarrow 4H^+ + 2O_2 + 4e^-$$
$$\text{Cathode} : 4H^+ + O_2 + 4e^- \rightarrow 2H_2O$$

5) Calculate the glucose concentration of the blood sample using the differential value of electric current.
   The detected electric current (rate current) is a function of time, and its peak value of differential waveform correlates with the glucose concentration (a, b and c in Figure 3).

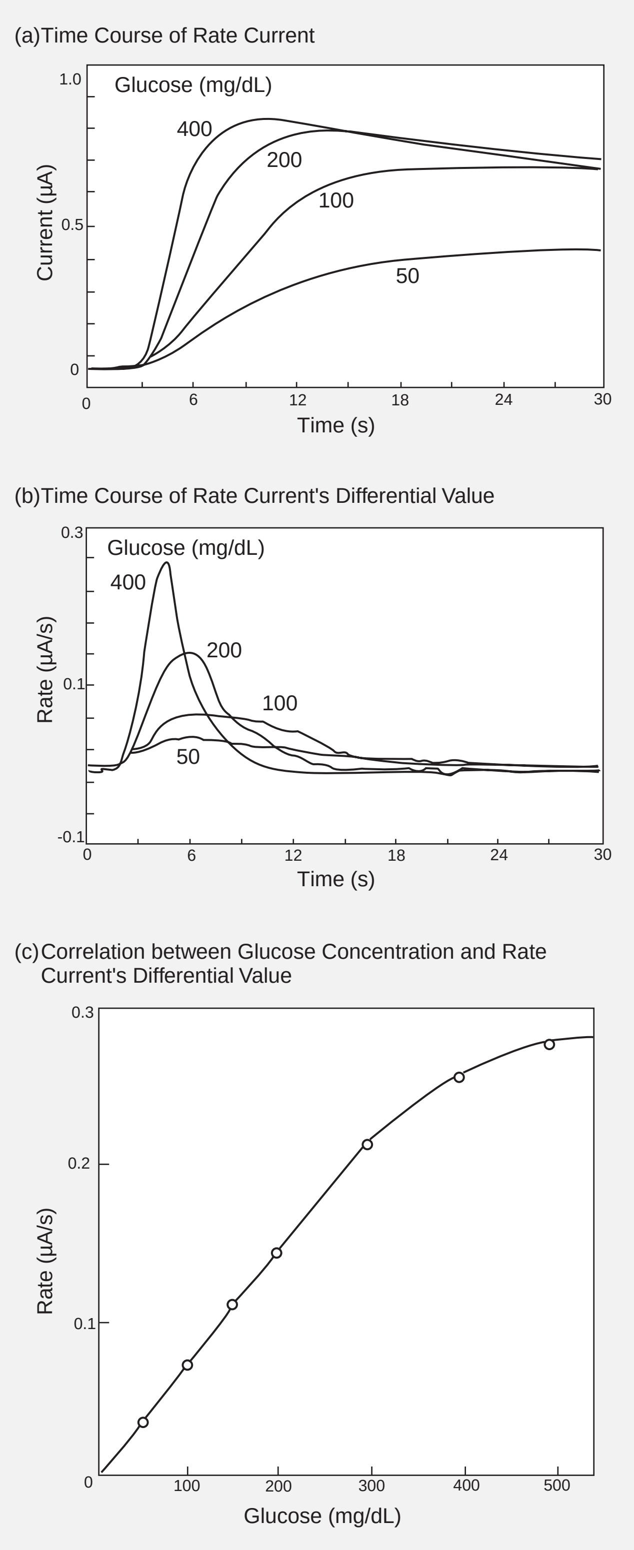

Figure 3 Measurement Principle and Data

Membrane Structures and Functions

Blood Cell Separating Membrane

The thin polycarbonate membrane has a certain number of hole whose diameter is tens of angstroms. It prevents blood cells and proteins from penetrating and allows only plasma components to penetrate, and simultaneously restricts their penetrating amount. Applying this functional membrane enables the whole blood measurement saving the work of pretreatment of blood sample. Only plasma components reacts on the sensor area and therefore the interference of hematocrit value*3 is avoided. Since the penetrating amount is restricted, the amount of oxygen required for oxidization on sensor part is supplied from the sources other than the sample blood (such as dissolved oxygen in cap membrane), and the interference of oxygen partial pressure fluctuation in the sample can be eliminated.

*3: Rate that the volume of red blood cells against the whole blood.

Cap Membrane

The sensor surface consists of diffusion-restricting membrane, glucose oxidase immobilized membrane and hydrogen peroxide permselective membrane. They are called “cap membrane” as a unit since the hydrogen peroxide electrode is capped by them.

- Diffusion Restricting Membrane

  The membrane is made of polyvinyl alcohol (PVA). It restricts the penetrating amount of glucose in the sample, prevents overrange of the detection sensitivity, and controls the measuring range.

- Glucose Oxidase Immobilized Membrane

  Glucose oxidase selectively reacts with glucose in the sample due to its reaction specificity. The glucose oxidase immobilized membrane is polyacrylonitrile (PAN) membrane which is chemically combined with glucose oxidase. It enables a long-time use of glucose oxidase, one of proteins, without degradation. It is also applicable to other measurement items when other kinds of enzyme are immobilized on it.

- Hydrogen Peroxide Permselective Membrane

  The membrane is made of acetylcellulose (AC). It restricts penetrating of electrode reactant (such as ascorbic acid) and eliminates disturbing factors from measurement data.

Hydrogen Peroxide Electrode

Structure

Figure 4 shows the structure of hydrogen peroxide electrode. It uses platinum to the work electrode (W)*4, silver to the reference electrode (R)*5 and counter electrode (C)*6, and has a thermistor inside the work electrode.

*4: The electrode applies voltage to induce redox reaction. In this application, it applies redox electric potential for hydrogen peroxide.

*5: The electrode is referred to when electric potential is applied to the work electrode. It has high resistance value in its circuit to keep out electric current.

*6: Redox reaction occurs on the electrode simultaneously with that on the work electrode.

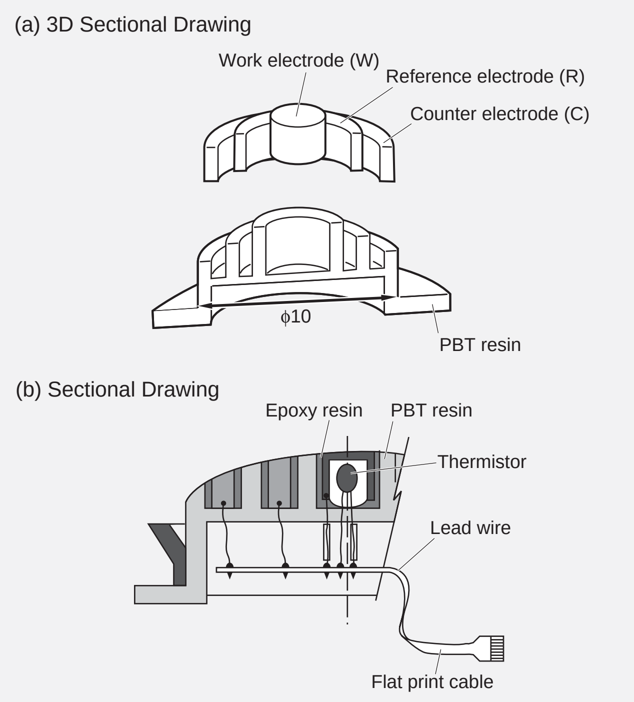

Figure 4 Hydrogen Peroxide Electrode

Electrode Control

Figure 5 shows the controlling pattern of applied electrode potential. Just before measurement, apply inverted potential and remove the oxide film from the electrode surface (refreshing) to clear it up. Again apply inverted potential (overshooting) and control the W-R interelectrode potential to swiftly become 0.75 V. The value is of the decomposition potential of hydrogen peroxide. The unit detects the completion of reaction after measurement, then turns to standby mode.

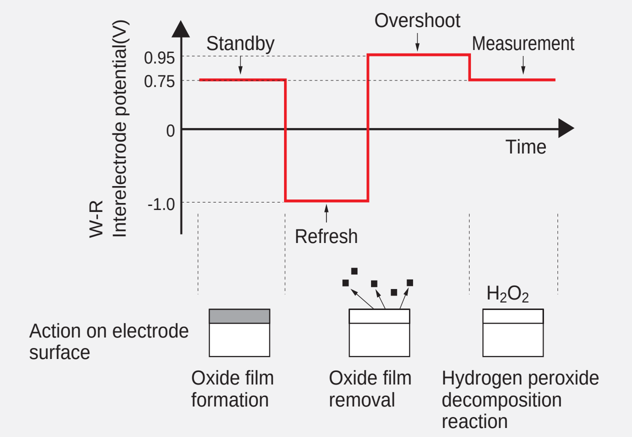

Figure 5 Controlling Pattern of Applied Electrode Potential

Antsense III Features

Sensor Surface Refreshing Mechanism

Antsense III achieves higher performance in the sensor surface refreshing mechanism in order to improve measurement accuracy and to have wider measurement range. Figure 6 shows the appearance of sensor surface refreshing mechanism.

After measurement, the unit intakes the reactant waste on the sensor surface into the storage liquid of buffer tank. Simultaneously it keeps the surface in optimum moist condition required for enzyme reaction, and reduces unreacted glucose on the surface. See the steps as follows:

1. Fit the sensor surface to the sponge*7 attached on the bottom side of buffer tank, and apply pressure so that the storage liquid penetrates the sponge to exude onto the sensor surface. The reactant waste on the surface is taken into the buffer tank.
2. Detach the sensor surface from the sponge and let it contact to air. Oxygen is supplied to the surface to

promote enzyme reaction of glucose oxidase and reduce unreacted glucose on the surface.

3. Repeat the above steps again to enable the sensor surface refreshing even after using high concentration sample (patent pending).

*7: It is in moist condition with the storage liquid, and retains the liquid to prevent from dropping.

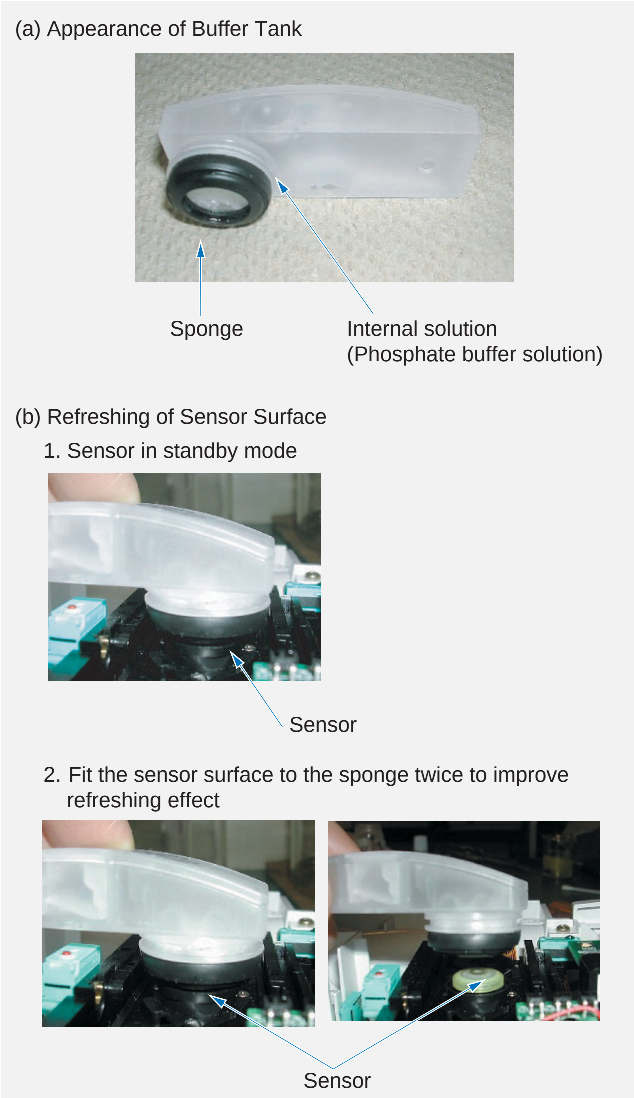

Figure 6 Refreshing of Sensor Surface

Performance

Figure 7 shows the measurement accuracy of glucose solution. The coefficient of variation is from 1.5 to 2.5%, in the concentration range from low to high. In measurement with actual samples, Antsense III has good correlation with Glucose Auto & Stat GA-1160[*8] through the range from low to high concentration (Figure 8).

*8: Glucose measuring device manufactured by Arkray and installed in many central laboratories. It is designed to measure a lot of samples in laboratory site using an immobilized enzyme electrode method (the same method as Antsense III).

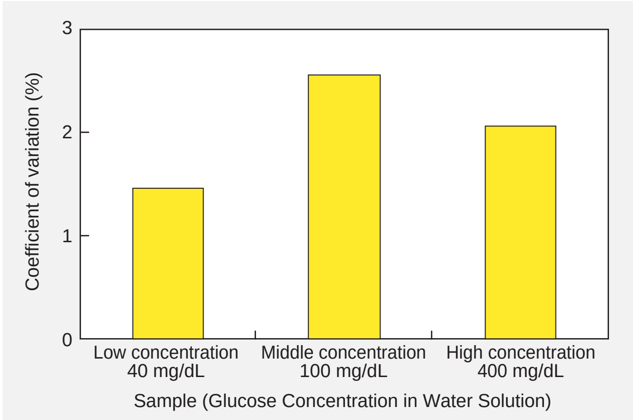

Figure 7 Measurement Accuracy of Glucose Solution

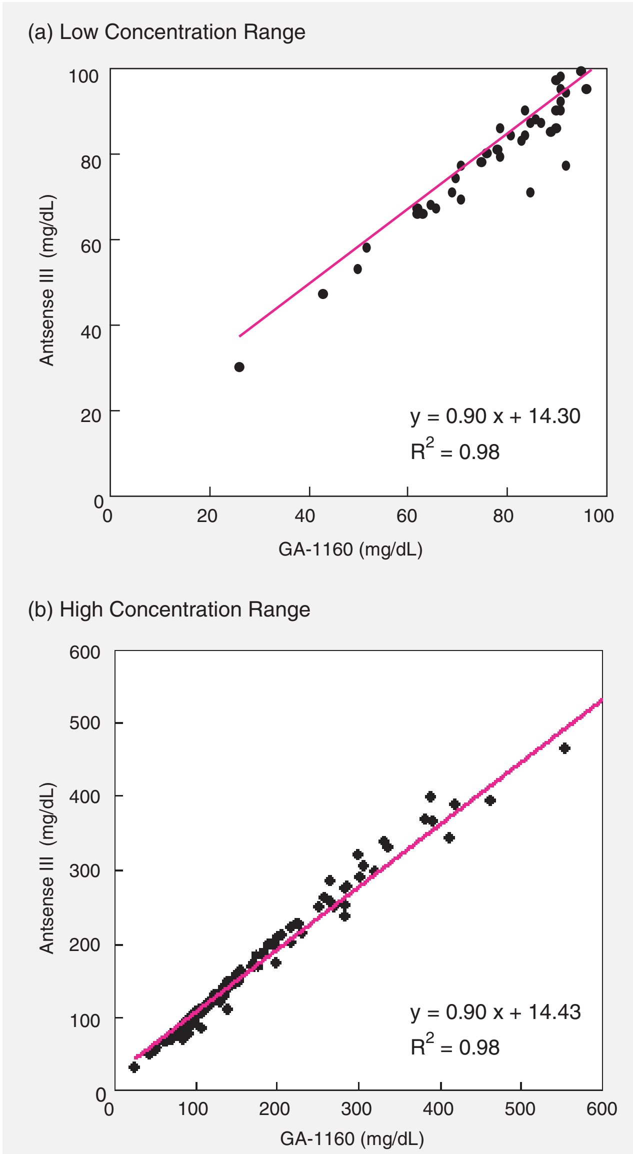

Figure 8 Correlation with Glucose Auto & Stat GA-1160 using Actual Samples

[Reference]

The measurement accuracy of Antsense II is evaluated and good correlation is reported with the reference model Glucose Auto & Stat GA-1140 (Figure 9).

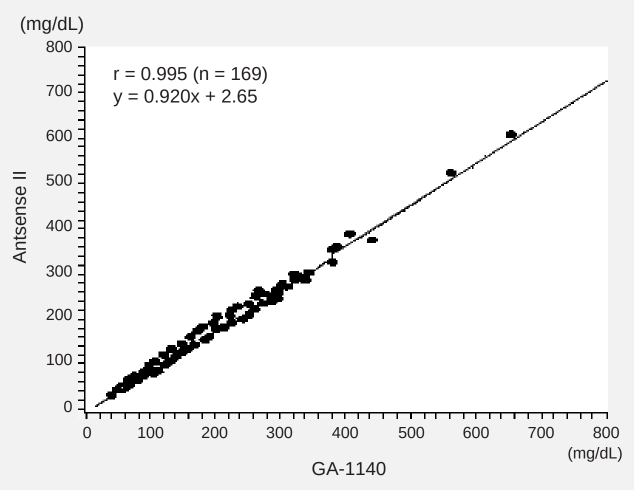

Figure 9 Correlation with Reference Model [1]

Usability

Generally in tests at hospitals, the values such as oxygen partial pressure and hematocrit of blood sample are unstable depending on patient’s condition and treatment method. Antsense III has an advantage of reducing the unstability with its hydrogen peroxide electrode method and blood cell separating membrane. It enables, even in in-situ diagnosis, the same method as a large-scale device which uses separated serum sample in laboratory, and ensures reliable measurement.

Conclusion

With more aging of population and rising of morbidity rate (due to lifestyle related diseases, etc.), the medical expenses have grown to a heavy burden on the Japanese national treasury. The situation requests the medical worksites for a drastic change. The same applies to HORIBA medical group and its business field of clinical inspection, and our efforts of cost reduction are inevitable. In near future, not only cost reduction in diagnosis and treatment at hospitals but streamlining of social works outside hospitals will be requested. At homes or offices, for instance, if a good care system for various patients’ conditions is established, patients’ quality of life will improve and social works relating to their hospital visits will be saved. At medical worksites where staffs always encounters emergency cases, a blood test immediately after sampling will enable appropriate treatment and promote patients’ recuperation, thus will save related social works. The key factor of future flexible testing is surely Antsense III and its series, the prospective point of care testing devices.

Reference

[1] Akiko Masuko, Ryuzo Abe, et al., Basic Discussion on the Improved Small-Size Electrode Type Blood Glucose Meter "Antsense II",

Journal of Medicine and Pharmaceutical Science 35(4), 921-928 (1996)

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