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Noninvasive Blood Glucose Concentration Monitoring Method with Suction Effusion Fluid by ISFET Biosensor

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SUCTION EFFUSION FLUID AS A BIOCHEMICAL CONSTITUENT SENSING SAMPLE

A small amount of body fluid can be extracted through the skin, drawn out by weak suction. Table 1 shows a comparison between suction effusion fluid and blood in rabbits.

It is clear that for low mol-wt substances, such as urea, uric acid, creatinine, or glucose, there are positive correlations between the concentration in the suction effusion fluid and that for blood. On the other hand, in the case of protein, which has large mol wt, or lipid, which is hydrophobic, concentrations in SEF are quite small, compared with that of blood. SEF contains about 20% serum lipid and half serum protein.

SEF is easily gathered by a weak suction (about 400 T_{orr}). Its flow speed is about 0.3 $\mu L/cm^2/min$. It is thought of as being blood filtered by capillary loops or skin, so that constituents included in this fluid can be explained by the scheme shown in Fig. 1.

This fluid was expected to be useful as a sample for continuous body fluid monitoring. If every measurement needed only a few μL of the sample fluid, a new blood constituent measurement method especially for blood glucose concentration can be established.

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Table 1
Composition Comparison Between Suction Effusion Fluid and Blood

	Blood serum (mean ± SD) $N=13$	Effusion fluid (mean ± SD) $N=13$
Glucose (mg/dL)	131 ± 18	139 ± 14
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.1
Urea-N (mg/dL)	15.3 ± 2.8	19.4 ± 4.4
Total lipid (mg/dL)	228 ± 76	39 ± 12
Total protein (g/dL)	5.1 ± 0.5	1.3 ± 0.4

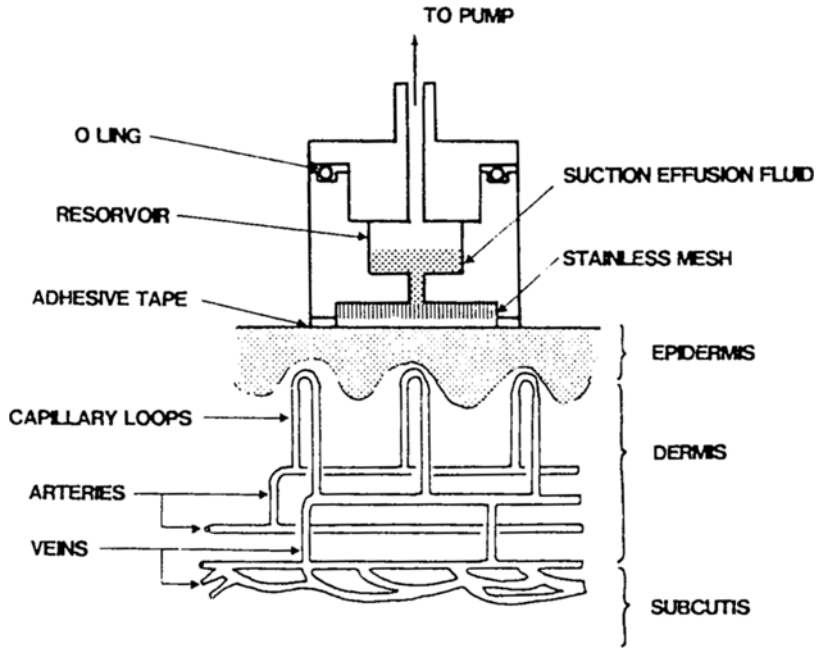

Fig. 1. Suction effusion fluid collection mechanism.

ISFET BIOSENSOR FOR BODY FLUID

The ISFET glucose sensor was fabricated as described in the previous report. Some improvements were carried out in membranes over ISFETs, as shown in Fig. 2. An enzyme FET(ENFET) membrane consists of two kinds of layers. The 1-μm thick lower layer is an enzyme immobilized membrane, consisting of spin coated enzyme, BSA solution, and glutaraldehyde solution mixture. The upper layer, which is also a spin coated membrane, but which does not contain enzyme, is a protective membrane to prevent serum protein adsorption onto the sensor. Furthermore, the reference FET (REFET) has the same membrane as the ENFET upper layer, to cancel any signal variation owing to serum protein adsorption by differential measurement.

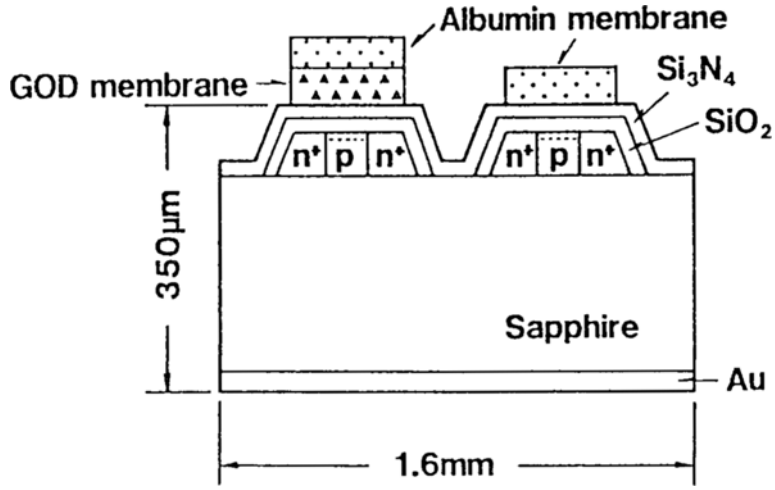

Fig. 2. ISFET glucose sensor cross-sectional view at sensing area.

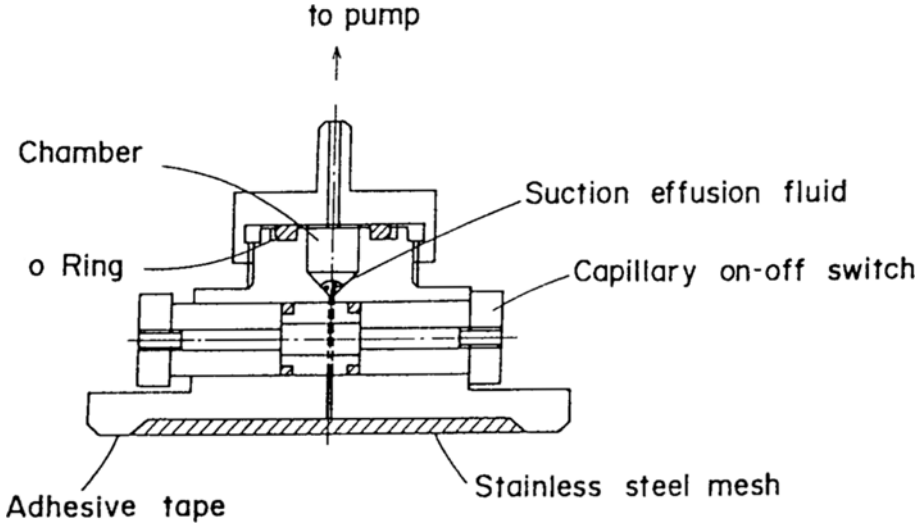

Fig. 3. SEF collecting cell.

SEF TECHNOLOGY APPLIED TO HUMANS

SEF Sampling Method

A SEF sampling cell used for application to humans, is shown in Fig. 3. The top if the cell was connected to a vacuum pump, whereby the cell was kept at 400 T_{orr} absolute pressure. The SEF was taken from the chamber by a syringe, after switching off the sliding cock, and opening a reservoir cap. After eliminating part of the volunteer's upper arm stratum corneum by adhesive tape treatment, the cell was fixed on the arm with Velcro tape.

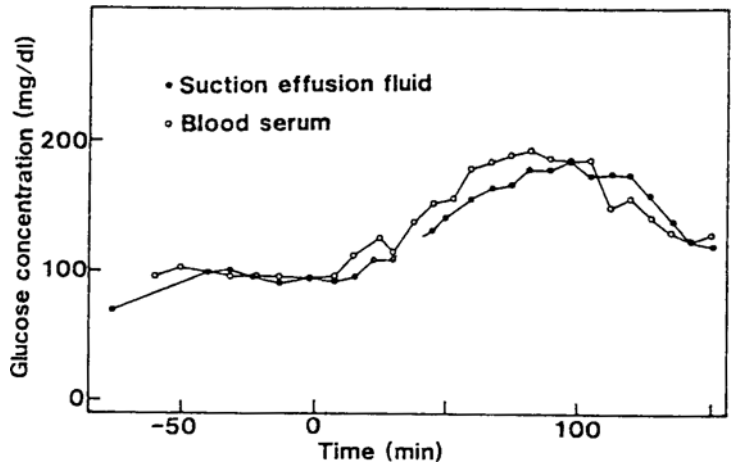

Fig. 4. OGTT result on human subject.

Effusion Fluid Glucose Concentration Measurement

Figure 4 shows the correlation between the effusion fluid glucose concentration, measured by the ISFET biosensor, and the blood glucose concentration, measured by a glucose analyzer during the experiment. The vertical axis represents glucose loading. The horizontal axis indicates time lapse, before and after oral 75 g glucose loading. This test was carried out on a healthy male volunteer, involving an impaired glucose load during a set time period. SEF and blood were collected every 7.5 min for about 3 h. Before the glucose load was induced, the glucose concentration in both the suction effusion fluid and the serum were constant and stable. After glucose loading, the SEF glucose concentration, measured by the ISFET biosensor, followed rather precisely that for the blood glucose, with an approx 10 min delay. The delay time can be assumed to be caused by sampling delay and the effusion delay for fluid passing through the epidermis. For cutaneous invasion caused by the tape stripping, the epidermis indicated mild redness and moisture without hemorrhage. This means that the proposed procedure is less invasive than conventional procedures (*1,2*).

REFERENCES

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2. Ito, N., Saito, A., Kuriyama, T., Kimura, J., Arai, T., Kikuchi, M., Kayashima, S., and Nagata, N. (1992), *Frontiers Med. Engng.* **4,** 35.