= 0.981, $S_{y|x}$ = 111 mg/L; mean plasma YSI = 1640 mg/L), averaging only 4% higher.

For glucose concentrations (570–4100 mg/L) measured in venous blood, the SureStep-Pro Hospital System (mean SureStep = 1540 mg/L) correlated well with whole-blood values measured by the YSI (SureStep = 1.18YSI − 5.08, n = 53, r^2 = 0.980, $S_{y|x}$ = 111 mg/L; mean blood YSI = 1350 mg/L), with SureStep-Pro values being 14% higher. In contrast, the SureStep-Pro Hospital System values not only correlated well but again closely matched plasma values determined by the Vitros 750 Analyzer (SureStep = 1.02Vitros − 2.81, n = 53, r^2 = 0.971, $S_{y|x}$ = 135 mg/L; mean Vitros = 1540 mg/L) and by the YSI (SureStep = 1.05YSI − 1.58, n = 53, r^2 = 0.973, $S_{y|x}$ = 130 mg/L; mean plasma YSI = 1480 mg/L).

Likewise, the SureStep-Pro Hospital System (mean SureStep = 1640 mg/L) correlated well with arterial whole-blood glucose values (580–3300 mg/L) measured by the YSI (SureStep = 1.08YSI + 3.38, n = 49, r^2 = 0.983, $S_{y|x}$ = 89 mg/L; mean blood YSI = 1480 mg/L), with SureStep-Pro values averaging 11% higher. For arterial plasma samples, the SureStep-Pro Hospital System values not only correlated well but closely matched those determined by the YSI (SureStep = 0.99YSI + 3.38, n = 49, r^2 = 0.983, $S_{y|x}$ = 88 mg/L; mean plasma YSI = 1620 mg/L).

In the capillary, venous, and arterial whole-blood samples with Hct determinations, we found no correlation between Hct and the difference between the SureStep-Pro Hospital System and YSI values. Fig. 1A shows the comparison of Hct and the difference between the SureStep-Pro Hospital System and Vitros values from venous samples. Similar findings were observed for capillary and arterial whole blood. Likewise, there was no correlation between the Po_2 and the difference between the SureStep-Pro Hospital System and YSI values in arterial whole blood (Fig. 1B).

The SureStep-Pro Hospital System has excellent day-to-day precision and is capable of measuring glucose concentrations in capillary, venous, and arterial whole blood. The SureStep-Pro Hospital System provides glucose values essentially equivalent to those obtained from plasma, with Hct and Po_2 having no effect on the results. Taken together, these studies demonstrate that the SureStep-Pro Hospital System provides highly accurate plasma-equivalent results on whole-blood samples. This approach should help eliminate possible confusion when comparing bedside meter results with those from the clinical laboratory.

References

1. 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. N Engl J Med 1993;329:977–86.
2. Brownlee M. Glycation products and the pathogenesis of diabetic complications. Diabetes Care 1992;15:1835–43.
3. Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's The pharmacological basis of therapeutics. New York: MacMillan Publishing Co., 1990:1475–80.
4. Holtkamp HC, Verhoef NJ, Leijnse B. The difference between the glucose concentrations in plasma and whole blood. Clin Chim Acta 1975;59:41–9.

Planar (Bio)Sensors for Critical Care Diagnostics, *Paul A. D'Orazio, Thomas C. Maley, Robert R. McCaffrey, Andy C. Chan, Donna Orvedahl, Joe Foos, David Blake, Sue Degnan, John Benco, Chris Murphy, Peter G. Edelman, and Hans Ludi** (Chiron Diagnostics, 63 North St., Medfield, MA 02052; *author for correspondence: fax 508-359-3955, e-mail hans.ludi@chirondiag.com)

Advances in planar (bio)sensors have allowed whole-blood diagnostics to be applied in testing close to the patient, resulting in rapid turnaround times, which are especially desirable in critical care settings. Several new technologies and custom chemicals had to be integrated to allow high performance, small sample size, fast response time, and cost-effective devices. (Bio)sensors described below are used for measurement of blood gases, blood electrolytes, glucose, and lactate in point-of-care environments.

Manufacturing of planar thick-film electrodes on ceramic wafers is now done with standard processes yielding precise patterns through the use of ultrapure metals for prolonged use-life under constant polarization. A platinized carbon paste ink has been developed to screen-print the active electrode of the glucose and lactate biosensor (Fig. 1, top).

In the amperometric sensor for Po_2, Nafion (polymeric perfluorinated ionomer; Aldrich) is used as an internal electrolyte and is spin-coated with a custom-made, patented polymer *[1]*. This polymer has a relatively low permeability for oxygen but is permeable to water vapor to allow fast wetting and a stable steady-state response signal (Fig. 1, middle).

For ion-selective sensors, a copolymer of methacrylamidopropyltrimethylammonium chloride and methyl methacrylate (MAPTAC/MMA) is used as a solid internal contact, resulting in minimal shifts in offset potential over >30 days *[2]* (Fig. 1, bottom)

For enzyme sensors, we applied a combination of an interference rejection cover membrane (FC 61 from Dow Corning) *[3]* and a correcting electrode to cope with known interferences *[4]*. The glucose and lactate sensor are virtually free of interference at maximum expected values of the individual substances being tested (see *[5, 6]* for examples). FC 61, a silicone material spun-cast from an aqueous emulsion, rejects interferences and has a restricted permeability for the substrates (glucose and lactate) but a high permeability for oxygen, making the sensor oxygen-independent over the Po_2 range of 25–700 mmHg.

For biosensors we also were required to apply enzyme-stabilizing agents, such as polyvinylalcohol, to achieve extended lifetime in a multianalyte, multiuse application. The sensors are polarized at ~+400 mV (vs Ag/AgCl). The use of platinum-activated carbon as the working electrode material permits these lower potentials to be used for the oxidation of hydrogen peroxide. The advantages of the lower operating potentials include a reduced interference from oxidizable substances in blood, which may permeate the FC 61 membrane, as well as the added benefit of extending sensor use-life (Fig. 1).

Except for lactate, all sensors show a use-life of >30 days for measuring 30 whole-blood samples per day. Accuracy is checked with NIST standards, where available, and values reported agree with those of accepted NCCLS Reference Methods, when such exist (see Table 1) *[7, 8]*.

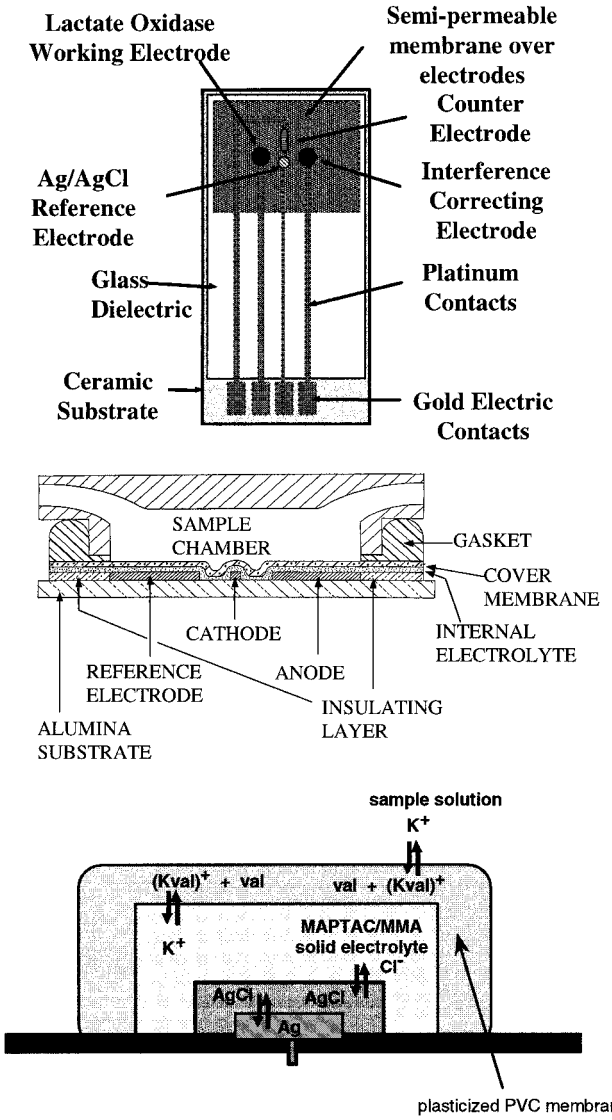

Fig. 1. Schematics of an amperometric biosensor (*top*), a planar oxygen sensor (*middle*), and a planar ion-sensitive sensor (*bottom*).

(*Top*) In the lactate sensor example, a cover membrane with limited diffusion for lactate, but unrestricted diffusion of oxygen, is required. As described above, FC 61 was found to optimally fulfill these requirements and, at the same time, act as an interference-rejecting membrane. To measure the presence and extent of interferences (mostly present as a combination of metabolites and drugs), a correcting electrode is used. Custom inks are used to apply the enzyme. (*Middle*) Two main components were necessary to be developed for an oxygen sensor to have a use-life of >30 days: a custom-made cover membrane that allows for rate-limiting oxygen and fast water vapor diffusion, and high-purity metal inks to avoid electrochemical reaction, such as the deposition of materials on the electrodes, which are polarized constantly at −800 mV. (*Bottom*) In the potassium sensor used as an example, the solid internal approach shown for a potassium sensor has to fulfill the function of an "internal fill solution" in a conventional three-dimensional electrode. In a planar format, the volume of the MAPTAC/MMA hydrogel layer is ~0.2 μL, compared with >100 μL in conventional electrodes. Stable offset potentials (<0.01 mV/min drift) over >30 days have been achieved.

Table 1. Sensor performance summary for whole-blood samples.[a]

Sensor	Measurement range	Use-life, days[b]	CV, %[c]
Glucose	0.5–55 mmol/L	60	6
Lactate	0–30 mmol/L	12	10
Po_2	0–600 mmHg	>30	1.5
Pco_2 (HCO_3)	10–150 mmHg	>30	2.5
pH	6.5–7.8	>30	0.008
Na	100–200 mmol/L	>30	1
K^+	0.5–15 mmol/L	>30	1
Ca^{2+}	0.2–5.0 mmol/L	>30	1.5
Cl^-	60–140 mmol/L	>30	1.5

[a] Performed with whole blood supplemented at three concentrations. A 9-sample, multifactorial experiment was run daily to determine precision, carryover, and dynamic range. The sensors were tested initially and at 30 days for selectivity and interferences.

[b] Determined by exposure to >1000 protein samples (serum or blood). Use-life was defined as meeting all performance specifications with respect to accuracy, precision, and selectivity. This was assessed by comparing performance with commercial systems (e.g., Chiron Diagnostics 860). Planar sensors performed at least equal to the commercial systems for whole blood, serum, and quality-control materials.

[c] Within-run precision in reference interval values in whole blood.

References

1. Foos JS, Edelman PG, Flaherty JE, Berger J. Extended use planar sensors. US Patent 5,595,646; 1997.
2. Chan AC. Material for establishing solid state contact for ion selective electrodes. Eur Patent Application 0 643 299 A1; 1994.
3. McCaffrey RR, D'Orazio P, Mason RW, Maley TC, Edelman PG. Clinically useful biosensor membrane development. In: Butterfield DA, ed. Biofunctional membranes. New York: Plenum Publishing, 1996:45–69.
4. NCCLS Document EP7-P. Interference testing in clinical chemistry; proposed guideline. Wayne, PA: NCCLS, 1986.
5. D'Orazio P, Parker B. Interference by the oxidizable pharmaceuticals acetaminophen and dopamine at electrochemical biosensors for blood glucose [Abstract]. Clin Chem 1995;41:S156.
6. D'Orazio P. Interference by thiocyanate on electrochemical biosensors for blood glucose [Letter]. Clin Chem 1996;42:1124.
7. Foos J, Blake D, Degen B, Taggliaferro D. New generation of solid-state sensors for electrochemical measurements: Na^+, K^+, Ca^{++}, Cl [Abstract]. Clin Chem 1996;42:S281.
8. Orvedahl D, Chan ADC, Murphy C, Fennyl S, Krouwer J. New generation of solid-state sensors for electrochemical measurements: pO_2 [Abstract]. Clin Chem 1996;42:S282.

Convergence of Three Methods to Resolve Discrepant Immunoassay Digitoxin Results, *Saeed A. Jortani,*[1] *Daniel Trepanier,*[2] *Randall W. Yatscoff,*[2] *and Roland Valdes, Jr.*[1]*([1] Dept. of Pathol. and Lab. Med., Univ. of Louisville, Louisville, KY 20292; [2] Dept. of Lab. Med. and Pathol., Univ. of Alberta, Edmonton, Canada; *author for correspondence: fax 502-852-1771, e-mail r0vald01@homer.louisville.edu)

We have observed significant analytical discrepancies (20% to 220%) in digitoxin (Crystodigin; DTN) immunoassay results for 11 serum samples from patients taking digitoxin. We used three methods—HPLC, immunoassay, and liquid chromatography electrospray mass spectrometry (LC/MS)—to investigate the possible sources of these discrepancies.