Special feature: Biosensors

In vivo chemical sensors for intensive-care monitoring

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Abstract—*There is a need for rapid assessment of a patient's biochemical status during intensive care so that therapies may be optimised. Chemical sensors for key species have the potential to allow continuous in vivo monitoring, and some progress is being made with certain sensors. Gases, ions and certain catabolites such as glucose and urea may be measured with devices based on mass spectrometric, electrochemical or optical principles. The physical form, and size of sensors must be matched to the measurement site, which can include the airway, the intravascular space, tissue and the skin surface. Electrochemical sensors for measurement of O_2, pH and glucose have been the most widely used to date, although fibre-optic devices are currently attracting considerable interest. Invasive sensors still suffer from the problem of poor biocompatibility, particularly devices used in arteries and veins. Noninvasive methods may be successful in certain circumstances and in some patient groups, but peripheral measurements are often significantly influenced by circulatory phenomena such as shock. Further research is required if these limitations of both invasive and noninvasive sensors are to be overcome and continuous chemical monitoring is to be established as a routine clinical technique.*

Keywords—*Biocompatability, Biosensors, Intensive care monitoring, In vivo sensors*

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1 Introduction

PATIENTS RECEIVING intensive care must be under continuous surveillance, in order that undesirable changes in their condition may be detected rapidly and appropriate therapeutic measures instigated. Such patients may have disturbances to one or several of their physiological control systems, such as renal, cardiovascular, respiratory, neurological or hepatic. The measurement and assessment of various physical parameters, such as blood pressure, blood flow or temperature, is important, and established methods for these are used widely with commercially manufactured sensors or transducers and associated electronic monitors.

Assessment of the biochemical status of the patient undergoing intensive care has, hitherto, largely been carried out by means of intermittent blood sampling and subsequent laboratory analysis. Of special interest and importance has been the assessment of blood gas and acid-base balance, and laboratory blood gas analysers have evolved over recent years to provide reliable, straightforward analysis of micro blood samples. Current generations of blood gas analysers also include the possibility of measuring potassium, calcium and sodium ions with inbuilt ion-selective electrodes. The inclusion of sensors for glucose and urea is also an achievable prospect.

The improvement of laboratory biochemical analysers through the use of sensors has led to the biochemical analysis being taken out of centralised laboratories and into the clinical arena, including hospital wards and intensive-care areas. This has significantly reduced the delay time in obtaining analytical results with the outcome that patient care may be optimised more rapidly. It would seem a logical step to attempt to monitor biochemical changes directly within the patient, and this represents the most challenging area for chemical sensor research.

The possibility of making chemical measurements directly within biological tissue was recognised several decades ago by physiologists (CLARK, 1956), physicists and engineers (KREUZER and NESSLER, 1958*a*; *b*; SILVER, 1965; LÜBBERS *et al.*, 1969; FATT, 1976). Early microsensors for the measurement of oxygen and pH provided important information for basic research, and indeed improved versions of the sensors are still utilised today. Transferring devices used for laboratory investigations into the clinical environment has been a difficult and lengthy process, and is still far from successful. Interactions which may occur between sensors and the biological milieu almost always have an adverse effect on the performance of the sensor, and in some cases may even jeopardise patient safety. The more detailed investigation of these interactions, and the subsequent amelioration of their effects, is necessary before the full potential of direct chemical monitoring in intensive care is achieved. At the same time, the further improvement of indirect or noninvasive methods represents an important parallel line of research.

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2 Needs for chemical monitoring

Patients requiring intensive care do so for a variety of reasons, but in every case they are considered to be critically ill and requiring rapid assessment of their condition to enable optimal treatment to be given. Patients having major surgery need careful monitoring during the surgical procedure as well as during the postoperative period. Quite often, casualty patients require intensive care, especially when head injuries have been sustained and when the cardiorespiratory system is impaired. These patients, and indeed others who may have various forms of cardiorespiratory disease, may require careful attention to their blood chemistry. Patients undergoing renal dialysis may either be receiving treatment at home or in a special renal unit, but in some cases patients in intensive care also require dialysis for acute renal failure. These patients, and those suffering liver failure will also require particularly careful assessment of their blood chemistry and *in vivo* chemical monitoring could be helpful.

Despite the complexities of the many physiological and biochemical control mechanisms, only a relatively small number of chemical variables will be required to be monitored continuously with *in vivo* sensors. Perhaps the most critical of all are oxygen, carbon dioxide and pH, for these have a direct bearing on the most fundamental processes of all, these being related to cellular metabolism and therefore viability. During certain forms of surgery there may be some value in monitoring anaesthetic gases and vapours such as nitrous oxide and enflurane, although there is no clear evidence that continuous monitoring will be beneficial. The measurement of ions such as sodium, potassium and calcium may also be beneficial in certain circumstances; for example the measurement of potassium ions could be useful in patients undergoing open-heart surgery. The monitoring of catabolites such as glucose, creatinine and urea is certainly important in some patients, for example those with diabetes or with renal failure, but these variables would not need to be monitored in all patients.

The chemical variables referred to may be measured in various anatomical sites. Gases and vapours can be monitored in the inspired and expired gas mixtures, but often it is necessary to make direct measurements within blood in arteries and veins, and for most ions direct blood measurement is essential. Similarly, the measurement of important catabolites must be carried out in arterial or venous blood. There is considerable interest in the measuremnt of some of these variables, especially oxygen, pH and glucose in tissue, including muscle. The main reason for this is the relative ease with which sensors may be inserted into tissue compared with arteries or veins.

3 Sensor characteristics

The shape, size and form of a particular sensor will be determined by the measurement site (ROLFE, 1988). Sensors for measurement in the airway may be relatively large, to be incorporated into ventilator tubing, face masks, or endotracheal tube connections. Direct arterial or venous measurements require sensors to be built into flexible catheters, and these may range from less than 1 mm to perhaps 2·0 mm in diameter. Measurements in tissues may be made with either relatively large needles, e.g. 0·8 mm diameter, or with microneedles having a diameter of a few microns for intracellular measurement. Measurement of certain gases may be made with devices attached to the surface of the skin (HUCH *et al.*, 1979), and such devices may be relatively large, of the order of 15–20 mm in diameter by 4–5 mm thick. Sensors used for *ex vivo* measurement within the extracorporeal circulation once again may be relatively large and similar in form to those used in airway monitoring.

For all but the skin surface application sensors must be supplied ready for use within sterile packaging. Methods of sterilisation include autoclave, gamma irradiation and ethylene oxide. The particular type of sensor will dictate the method of choice, an important consideration being the materials from which the sensor is constructed. Polymer and metal components of the sensor may be affected by heat, chemical attack or by radiation, and all of these factors must be borne in mind when practical devices are being developed.

Naturally the sensors must provide appropriately accurate measurements, and this needs to be judged for each particular application. Sensors will generally require initial calibration, with subsequent calibration checks being carried out as and when possible. Sensors used within *ex vivo* circulation loops or within mechanical ventilators may be removed relatively easily, either for calibration or to be discarded if they cease to function adequately. On the other hand, sensors inserted into arteries and veins cannot be easily removed, and must be calibrated *in situ*.

4 Sensor principles and designs

In spite of the importance of continuous chemical monitoring in various patient groups undergoing intensive care, surprisingly few systems are being used successfully as a routine. Nevertheless, it is instructive to consider the different approaches which have been investigated, in order to reach firm conclusions regarding major problem areas requiring further research.

4.1 *In the airway*

Measurement of oxygen and carbon dioxide in the airway of a patient being mechanically ventilated can be useful for management of the therapy. In addition, during anaesthesia there is some value in being able to measure the airway concentrations of the anaesthetic agent, which may be nitrous oxide, halothane or enflurane.

Gaseous oxygen can be measured with electrochemical cells in which a potential of approximately −600 mV applied to a noble metal (gold, silver, platinum) cathode with respect to a reference electrode (e.g. silver/silver chloride) reduces oxygen producing a current proportional to oxygen partial pressure pO_2. The cathode, reference electrode and electrolyte are contained within a thin gas-permeable membrane, and this ensures the reliable control of diffusion of oxygen towards the cathode surface (CLARK, 1956; CLARK *et al.*, 1953). The cathode potential may be derived externally, or may be generated internally in the case of a galvanic cell (MANCY *et al.*, 1962). In this case a silver cathode is combined with a lead anode, and this couple is sufficient to generate the appropriate polarising voltage.

Electrochemical oxygen monitors are used widely in neonatal intensive care for monitoring inspired oxygen concentration in ventilators or oxygen concentration hoods. Difficulties arise in the use of electrochemical oxygen sensors in the presence of anaesthetic agents, due to the fact that such agents are often electroactive. For example, nitrous oxide and halothane can be electrochemically reduced at a silver cathode, and this will contribute to the oxygen current, producing a non-specific signal (SEVERINGHAUS *et al.*, 1971). One way of addressing this issue is to polarise the sensor cathode in a pulsatile fashion (SHORT and SHELL, 1985), first to a potential for oxygen reduction and, for example, secondly polarising the

cathode at a potential optimised for nitrous oxide reduction. This then allows a single sensor to be used for the simultaneous measurement of two or even three gases (HAHN *et al.*, 1979). It is also feasible to reduce carbon dioxide electrochemically if an organic solvent, such as di-methyl sulphoxide (DMSO), is used in the electrolyte.

Most electrochemical sensors for inspired gas monitoring have response times (95 per cent) between 20 and 60 s. It is feasible to use a very thin gas-permeable membrane and achieve a much more rapid response time, e.g. 1 s (ROLFE, 1976), but such sensors have limited operational lifetime and poor long-term stability. If rapid response time is needed for inspired gas monitoring then alternative techniques will be required.

The paramagnetic properties of the oxygen molecule allow accurate measurement in the gas phase (ELLIS and NUNN, 1968). A sample of the gas is aspirated into a dumb-bell shaped chamber suspended in a magnetic field. Rotation of the dumb-bell is then used as a measure of oxygen concentration, and a 90 per cent response time of 10 s can be achieved. The gas sample must be dried by means of a silica-gel column, and this can introduce a delay in response. Nevertheless, the paramagnetic oxygen analyser is a reliable and accurate technique for continuous gaseous oxygen monitoring.

Mass spectrometry is perhaps one of the most versatile analytical techniques of relevance to gas monitoring. Its importance was recognised in the early 1960s (WOLDRING *et al.*, 1966), the key advantage being the ability to measure several gases simultaneously. A continuous sample of the respired gases is aspirated through a flexible cannula into the inlet system of the spectrometer. The response time of the analysis is of the order of 100 ms, and flow through the cannula may introduce a fixed delay of approximately 100 ms. The cannula may be constructed of stainless-steel, and typically is electrically heated to prevent condensation of water vapour. Magnetic sector machines tend to be relatively large and immobile, and therefore instruments employing a quadrapole analyser may be preferred.

The main disadvantages of mass spectrometry are the relatively high capital cost and the fact that technical support is required to ensure a reliable service. Costs may be offset by employing a single mass spectrometer, together with a multiplexed sampling system, to allow many patients (e.g. 10) to be monitored quasi-simultaneously.

In spite of its advantages of flexibility and rapid response time, mass spectrometry is not widely used for routine intensive-care monitoring.

The most widely used technique for respiratory CO_2 analysis is based upon the infra-red absorption properties of carbon dioxide. Absorption of radiation involves a transition in a molecule between discrete energy levels, and the wavelength of the radiation absorbed equates to the energy difference. The main types of absorption process are: electronic transitions at 0–1·5 μm; bond vibrations at 1·5–30 μm; rotations of molecules at 30–1000 μm. In practice the gas for analysis will be drawn into a sample tube, and a differential optical absorption measurement will be made between this and a reference tube. The absorption measurement is carried out by allowing the infra-red light transmitted through the sample and reference tubes to be absorbed in two gas-filled detector units positioned either side of a flexible diaphragm. Absorption of light in the detector unit leads to a temperature increase with subsequent expansion, and thus differential pressure measurement in proportion to CO_2 concentration is made. More recent CO_2 monitors merely use infra-red detectors to measure the absorption by the sample gas.

Other gases and vapours absorb infra-red radiation, and therefore CO_2 measurements may need allowance made for this. However, this also means that the anaesthetic agents may be measured, provided specific absorption bands can be identified. For CO_2 measurement 4·26 μm is used, and 3·9 μm for nitrous oxide.

Recently a photoacoustic spectroscopy technique was introduced as the basis of a combined O_2, CO_2 and anaesthetic agent monitor (B&K, Denmark, type 1304 anaesthetic gas monitor).

4.2 *Intravascular sensors*

Invasive measurement of the concentrations of biochemicals in blood can often provide the most direct, and rapid, indication of clinical condition. Improvement or

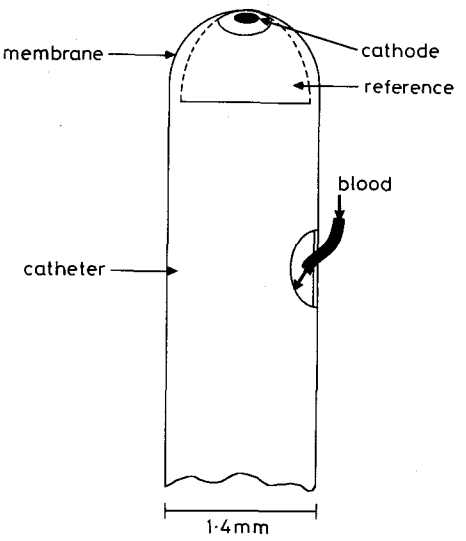

Fig. 1 *A catheter-tip pO_2 sensor. Blood may be sampled via one lumen, while electrical connections to the cathode and reference pass along a second lumen to an external connector*

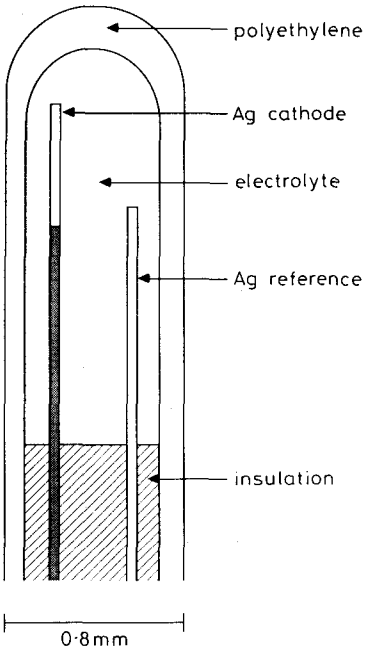

Fig. 2 *A pO_2 sensor designed for insertion into an adult peripheral artery (MINDT, 1973)*

deterioration in a patient's cardiorespiratory status could be detected quickly by means of continuous arterial O_2, CO_2 and pH measurement if suitable intravascular sensors were available. Several attempts have been made to develop such sensors for routine clinical use, but only limited success has been achieved to date, in spite of optimistic reports from research groups.

Intravascular sensors must mostly be constructed in the form of flexible catheters or cannulae, with dimensions appropriate for insertion into either a peripheral or central vessel (Fig. 1). In adults there may be some opportunities for insertion into the radial or brachial arteries, or via a femoral artery or vein to gain access to the central major vessels. In critically ill newborn babies it is common practice to insert a catheter into the umbilical artery, and sometimes the vein, to access the central vessels. In all of these situations, with subjects ranging from small newborn babies through to adults, the dimensions of the sensors range from 0·5 mm to perhaps 2·0 mm diameter (Fig. 2).

4.2.1 *Gases*: Oxygen partial pressure pO_2 may be most easily measured electrochemically, as described above in Section 4.1. The basic membrane-covered amperometric oxygen electrode needs to be attached to a suitable catheter, and selection of materials and mechanical design is of utmost importance to ensure safe and reliable operation. Since Clark's invention of the membrane-covered oxygen electrode many groups have developed catheter-tip devices (KREUZER and NESSLER, 1958*a*; *b*; CHARLTON *et al.*, 1963; KROG and JOHANSON, 1959; SAID *et al.*, 1961; KOEFF *et al.*, 1962; GODDARD *et al.*, 1972; PARKER *et al.*, 1971; HUCH *et al.*, 1973; MINDT, 1973; ROLFE, 1976; JANSEN *et al.*, 1978). Each of these designs employs a particular approach to solving the problem of attaching the sensor, and especially the membrane, safely and securely to the catheter tip, and these have been reviewed elsewhere (ROLFE, 1976). The methods include 'O'-ring fixation, screw-cap, snap-cap, push-on collar and dip-coating. To achieve a smooth external surface, which is important in relation to haemocompatibility, membrane attachment by 'dip-coating' appears to have certain advantages. This method also allows membrane thickness to be varied, and thus alter sensor response time, simply by varying the number of coats applied and the viscosity of the polymer solution. This approach is possible with a number of relevant polymers, such as the polyurethanes, polystyrene and the polyvinyl chlorides.

The initial animal evaluations of the sensors reported above have mostly been encouraging, with the demonstration of interesting temporal changes in arterial pO_2. However, the potential for problems with clotting had often been recognised in advance, and the animals therefore heparinised. This of course has implications for ultimate clinical use.

Blood oxygen monitoring may also be carried out with optical sensors, and the first approach towards this was with fibreoptic oximeter catheters for arterial, mixed venous or intra-cardiac oxygen saturation measurement. The absorption spectra of oxyhaemoglobin HbO_2 and deoxyhaemoglobin Hb allow the relative proportions of these two components to be measured, thus giving oxygen saturation:

$$O_2 \text{ saturation} = HbO_2/(Hb + HbO_2) \times 100 \text{ per cent}$$

ENSON *et al.* (1962) designed a system comprising a cardiac catheter containing a fibre-optic bundle to be inserted through a needle. This earlier design was further developed by commercial organisations, e.g. Oximetrics, using polymer optical fibres contained within polyurethane catheters. Good performances have been achieved with these devices in newborn babies (WILKINSON *et al.*, 1978). A combined fibre-optic oximeter and pO_2 sensor has also been reported (PARKER, 1981; Fig. 3).

Oxygen in blood may also be measured with a sensor based on fluorescence (Fig. 4). A fluorescent dye, such as perylene dibutyrate, is adsorbed to organic beads contained within a hydrophobic gas permeable membrane. The dye is excited with blue light (468 nm) and it emits radiation at 514 nm (green), and pO_2 is calculated from the relationship:

$$pO_2 = \text{const } \{(\text{blue/green}) - 1\}^m$$

The choice of dye is important to optimise sensitivity and brightness (PETERSON *et al.*, 1984).

The matter of monitoring other gases directly within the vascular system has been more problematical than for oxygen. Most interest has been in the measurement of

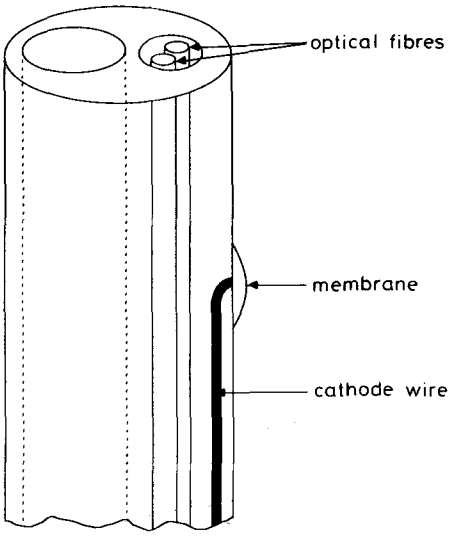

Fig. 3 *This catheter sensor combines optical fibres for oxygen saturation measurement with an electrochemical pO_2 sensor. The latter utilises a remote reference, with an ion-permeable membrane covering the cathode tip (PARKER, 1981)*

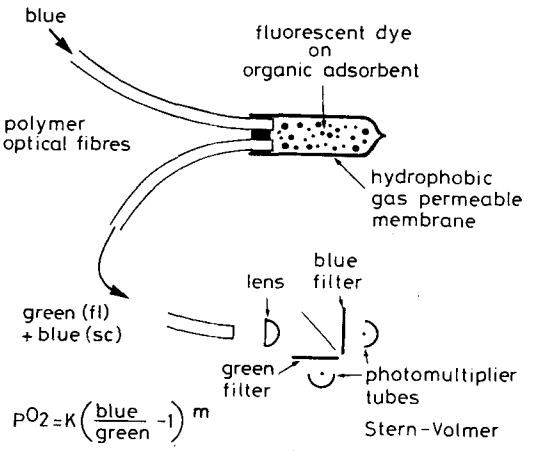

Fig. 4 *The phenomenon of fluorescence quenching by oxygen is utilised in this intravascular pO_2 sensor (from ROLFE, 1988, with permission)*

pCO_2, with electrochemical potentiometric sensors for pH surrounded by a CO_2-permeable membrane, the Stow-Severinghaus electrode (STOW and RANDALL, 1957), being the most popular approach. The use of a glass pH electrode in this design (PARKER *et al.*, 1978) presents constructional problems, and metal/metal oxide pH sensors have also been tried, using antimony, iridium or palladium (COON *et al.*, 1976). As has been mentioned above for airway monitoring, it is also possible to measure CO_2 with an amperometric sensor in which the electrolyte is non-aqueous, e.g. dimethyl sulphoxide. However, in practice such sensors are extremely difficult to construct due to the aggressive nature of the solvent.

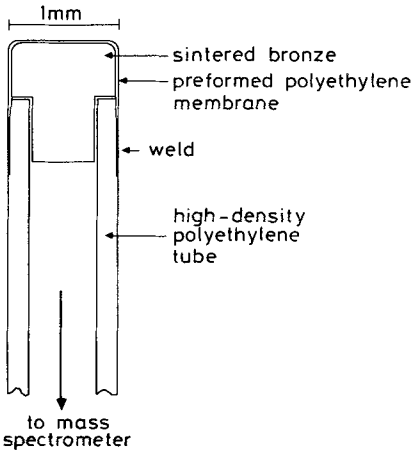

Fig. 5 *An intravascular sensor for connection to a mass spectrometer. The sintered bronze plug supports the pre-formed membrane, to resist the high vacuum of the mass spectrometer inlet*

Mass spectrometry has already been referred to above as a means with which several gases such as O_2, CO_2, N_2 and N_2O may be measured simultaneously. The feasibility of using a mass spectrometer for intravascular gas monitoring was first described by WOLDRING *et al.* in 1966. Further developments of sensors were described by OWENS *et al.*, in 1969 and by BRANTIGAN *et al.* in 1976. The basic approach is to use a gas-collection cannula having a supported membrane at its tip. The sensor shown in Fig. 5 was developed from the concept of welding pre-formed polyethylene membranes to a supporting thick-wall high-density polyethylene tube, originally used in an electrochemical pO_2 sensor (ROLFE, 1976). The tubing must have the strength to withstand the mass spectrometer inlet vacuum, and be relatively impermeable to gas diffusion. Other designs have been described, and stainless-steel (Fig. 6) has been used for the connecting cannula by PINARD *et al.* (1978), and by LUNDSGAARD *et al.* (1978; 1980), whereas PARKER and DELPY (1983) employed a nylon catheter coated on the inside with polyurethane.

The performance of the mass spectrometer sensor is mainly determined by the gas-diffusion membrane, because this controls gas throughput into the mass spectrometer cannula, and will therefore influence sensitivity, response time and depletion (GRØNLUND, 1978). Highly permeable membrane materials, such as silicone rubber or latex rubber, produce rapid response time but lead to a depletion error. Response times in the region of 1 min have been achieved with PTFE and polyethylene membranes, and depletion errors were maintained at an acceptable level (BRANTIGAN *et al.*, 1976; PINARD *et al.*, 1978).

4.2.2 *Ions:* Electrochemical techniques have been the most popular to date for intravascular monitoring of ions, although at present there is also considerable interest in optical methods. Potentiometric ion-selective sensors are those in which a potential difference across a membrane is used to detect the difference in ion activity between an internal reference solution and the external sample solution. The membrane potential difference E is given by

$$E = E_0 + RT/F \ln (a_i + K_{ij} a_j)$$

where E_0 is the standard potential, R is the universal gas constant, T is absolute temperature, F is Faraday's constant, a_i is the activity of the desired ion, K_{ij} is the selectivity coefficient and a_j is the activity of an interfering ion.

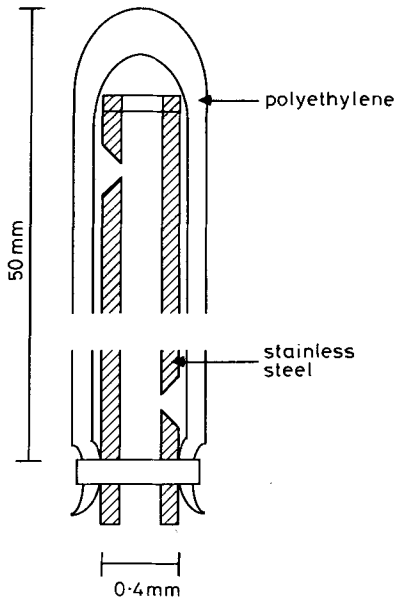

Fig. 6 *An intravascular sensor for use with a mass spectrometer, the diffusion membrane supported by a slotted stainless-steel tube*

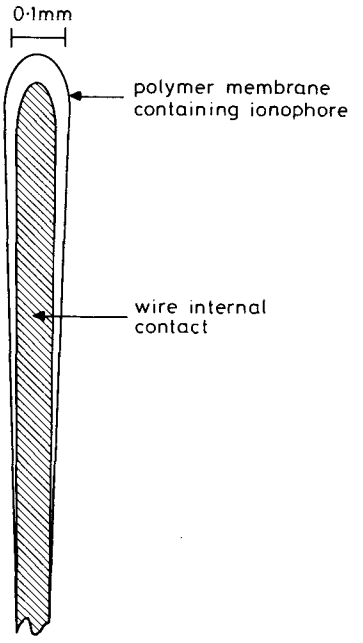

Fig. 7 *A micro ion-selective sensor, employing a dip-coated polymer membrane containing an ionophore*

Glass membranes may be used for a wide variety of cations and anions, but most interest in intensive-care monitoring has been focused on H^+ and K^+.

BAND and SEMPLE (1967) reported the use of a glass pH electrode which could be inserted into an artery through a modified needle. Blood was allowed to escape back through the needle at a controlled low rate so that the electrode could respond to rapid changes in arterial pH. The fragility and constructional difficulties associated with glass membranes have encouraged several groups to consider the use of polymer membranes. This approach was pioneered by Moody and Thomas in the 1960s (CRAGGS *et al.*, 1974), who developed a Ca^{2+} sensitive membrane employing polyvinyl chloride. Work has continued with the incorporation of neutral ion carriers (MORF and SIMON, 1977). These polymer membranes appear attractive because there is the potential of very simple construction; merely by dip-coating a reference wire into the membrane solution the coated wire ion selective electrode (CWISE) can be produced (Fig. 7).

A flexible catheter K^+ sensor with potential for intravascular and myocardial use was described by HILL *et al.* in 1978. The antibiotic valinomycin was used as the ionophore, the supporting membrane being cast from PVC in tetrahydrofuran. The membrane solution was dispensed onto a glass plate, and after the THF had evaporated 0·2–0·4 mm thick membranes were produced. These were then cut into disks and placed over the end of a PVC catheter.

Miniature K^+ sensors have been constructed by attaching PVC membranes containing valinomycin to fine silver wires (SMITH *et al.*, 1973), but these were not used for *in vivo* measurement. The design included a reference medium of KCl in polyvinyl alcohol beneath the cast valinomycin-PVC membrane with the aim of achieving a thermodynamic definition of the electrode operation.

Polymer membranes for pH sensors have been investigated by several groups. Tridodecylamine (TDDA) has been incorporated into a PVC matrix, and used in a microsensor for intracellular pH measurement (AMMANN *et al.*, 1981), and also in a sensor for foetal pH assessment (MARTIN *et al.*, 1985; O'DOWD *et al.*, 1988). LE BLANC *et al.* (1976) used p-octadecyloxy m-chlorophenyl hydrazone mesoxalonitrile (OCPH) dissolved in a block co-polymer, polysiloxane and poly (bis phenol-A carbonate) as a pH membrane for an intravascular sensor, and this material has subsequently been used by others (COBBE and POOLE-WILSON, 1980). In most cases a reference electrode is connected by a salt bridge to the intravascular space, although skin-surface mounted Ag/AgCl electrodes have also been employed.

A satisfactory, theoretical explanation for the function of the CWISE has not yet been agreed, due to the thermodynamic uncertainties of the processes occurring at the interface between the membrane and the internal reference wire surface. The sensor designed by COBBE and POOLE-WILSON (1980), a catheter-tip pH device, used OCPH in a PVC membrane which was dip-coated onto a ceramic plug inserted into the tip of a 0·9 mm diameter polyethylene tube. An internal electrolyte containing either hydrochloric acid, or a solution of sodium chloride, sodium citrate and citric acid was used. A silver/silver chloride wire was used as the internal reference electrode, and the overall tube stiffness was increased by incorporation of a fine steel stylet. The sensor could be inserted through a cardiac catheter, and it has been used in animal research and in humans. COBBE and POOLE-WILSON have reported results from their sensors when used for continuous coronary sinus and arterial pH monitoring during pacing-induced ischaemia in coronary artery disease (1982). In these studies a conventional calomel reference electrode was connected to the line flushing the catheter with heparinised saline.

The polymer pH membrane was also used in a combined pH and pCO_2 sensor manufactured by Biochem International. This miniature sensor comprises an outer OCPH membrane for the measurement of blood pH, and a palladium/palladium oxide pH sensor, together with a saline bicarbonate solution and silver/silver chloride reference electrode within the OCPH membrane for pCO_2 measurement. The OCPH transmembrane potential is measured between the internal Pd/PdO electrode and an external reference electrode which may be attached to the patient's skin surface. This combined sensor has been used in human studies, during anaesthesia and surgery, and good results have been reported (COON *et al.*, 1976; SUGIOKA, 1981).

The metal/metal oxide electrode is also of interest for pH measurements *per se*. Most work of relevance to intensive-care monitoring has been carried out with antimony and iridium. EDWALL and NILLSON (1981) have carried out extensive work on the investigation and use of antimony oxide pH electrodes. The voltage produced by the Sb/Sb_2O_3 electrode is considered as a corrosion potential, determined by two reactions, anodic and cathodic. Variations in pO_2 can therefore influence the electrode potential, but Edwall has shown that the use of a monocrystalline antimony electrode can produce sensitivity and stability suitable for long-term monitoring (EDWALL, 1978).

The use of iridium/iridium oxide as an implantable pH electrode was first described by CAMMILLI *et al.* in 1978. They showed that the pH sensor could be implanted in the right ventricle of rat and a silver/silver chloride reference electrode placed under the skin of the animal, to achieve stable pH response over a 40-day period of implantation. This approach has been further investigated through the use of film electrodes (DE ROOIJ and BERGVELD, 1981). This iridium/iridium oxide film pH electrode was shown to have fast response, low electrode impedance, and very low influence by pO_2.

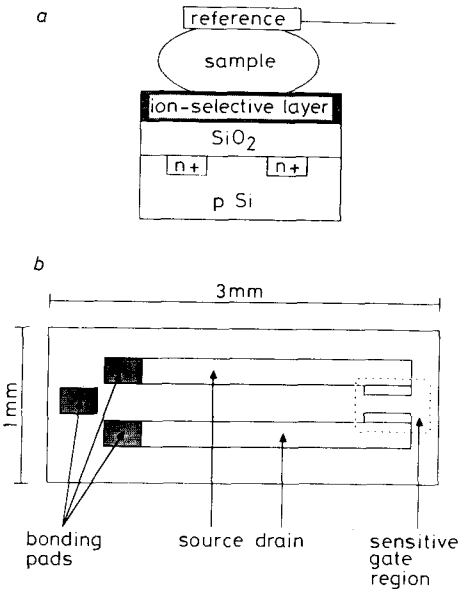

Fig. 8 *(a) Schematic of an ion-selective field-effect transistor, with the sample in contact with the selective layer and a reference electrode. (b) Plan view of a stretched ISFET, designed to maximise the spacing between the 'wet' sample region and the electrical connections*

The ion-selective field-effect transistor (ISFET) has attracted considerable interest since it was first described by BERGVELD (1970), offering the potential of low-cost, reliable microminiature sensors. The basic concept of the ISFET is that of a high input impedance potential measuring device, achieved in practice by the removal of the metal gate region normally present in a field-effect transistor. The potential applied at the gate, derived through an ion-selective process, modulates the current between the source and the drain. The silicon dioxide layer has a basic pH sensitivity, but silicon nitride over the surface of the silicon dioxide yields better sensitivity and stability. Much effort has been required in recent years to achieve satisfactory encapsulation of ISFETs to combat deterioration of the electrical characteristics resulting from water vapour ingress.

The small dimensions of ISFET devices allow catheter sensors to be produced, and devices for both pH and pCO_2 have been described (SHIMADA *et al.*, 1980). The ISFETs are constructed in the form of needles by means of anisotropic etching of the silicon substrate (ESASHI and MATSUO, 1978). The catheter pH ISFET is 1·05 mm diameter, the chip being embedded in silicone resin at the tip of a nylon tube, with a hydrogel coating over the surface said to improve the blood compatibility. Conversion of this basic device for CO_2 monitoring was achieved by incorporating a silver/silver chloride reference on the chip, depositing polyvinyl alcohol gel containing NaCl and $NaHCO_3$ over the ISFET and reference, and finally coating both regions with a thin silicone resin. Although such devices have been used for intravascular measurements, both in animals and humans, operation for periods of more than 24 h has generally been difficult to achieve due to encapsulation difficulties. ISFET sensors have also been developed for potassium ion measurement, the gate region being covered either with a glass potassium-selective membrane or with a valinomycin-PVC polymer membrane (Fig. 8).

The optical approach of sensing, as described for oxygen measurement, may also be used for pH sensors. SAARI and SEITZ (1982) described a pH sensor in which fluorescence intensity of immobilised fluoresceinamine at 520 nm is measured following excitation at 480 nm. Improvement in sensor performance was achieved through the use of ratio measurements of fluorescence intensity with excitation at 410 nm and 460 nm, using the dye hydroxypyrene trisulphuric acid covalently bound to a cellulose matrix (GEHRICH *et al.*, 1986). These authors have described a single device containing optical sensors for pH, pCO_2 and pO_2, together with a thermocouple for temperature compensation. An alternative to fluorescence measurements for pH is to measure optical absorption, for example by the dye phenol red immobilised within a gel matrix or to organic beads, and contained within an H^+ permeable membrane (PETERSON *et al.*, 1980). An important problem reported with fluorescence and absorption type optical sensors is that of interference from anaesthetic agents, and this problem will need to be addressed before such sensors can be used in patients during or immediately after surgery.

4.2.3 *Glucose*: Of the more complex biochemical species which may be measured with sensors or biosensors, glucose is the one analyte for which a case has been made for monitoring during certain intensive-care situations. The need for glucose-sensitive devices can be most readily met with biosensors in which an enzyme is used to achieve selective recognition of the glucose molecule (GUILBAULT, 1982). The enzyme glucose oxidase has been used by many groups, and the following reaction is employed:

$$O_2 + \text{glucose} \rightarrow \text{gluconic acid} + H_2O_2$$

This reaction can be followed if the glucose oxidase is immobilised over the surface of an electrochemical sensor able to measure oxygen, hydrogen peroxide or pH. The rate of formation of hydrogen peroxide can be measured as the steady-state current following oxidation at a platinum anode. Fig. 9 shows a catheter-tip glucose sensor in which a platinum anode and a surrounding silver/silver chloride cathode are attached to the tip of a polyurethane catheter (REA *et al.*, 1985*b*). The anode and cathode are first coated with cellulose acetate, the purpose of which is to restrict the diffusion of interferents to the anode. Glucose oxidase, immobilised within cellulose acetate is then dip-coated over this in a membrane, and finally a polyurethane membrane is dip-coated over the complete sensor tip. This device has a 90 per cent response time of 48 s, and an *in vivo* linear drift of 0·8 per cent per hour. Enzyme sensors based on glucose oxidase are theoretically oxygen dependent, although in practice fluctuations of venous pO_2 do not introduce any significant error in the glucose measurement. However, a considerable amount of research has been carried out by several groups to eliminate oxygen dependence through the use of an electron acceptor, and the use of ferrocene has been successfully employed for this purpose (CASS *et al.*, 1984).

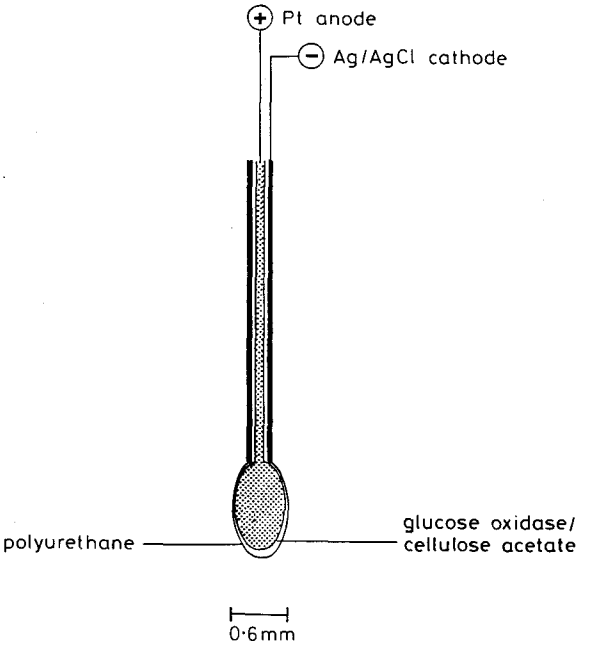

Fig. 9 *A needle glucose sensor (REA et al., 1985b)*

An optical glucose sensor has been described based on the use of competitive binding (SCHULTZ *et al.*, 1982; MANSOURI and SCHULTZ, 1984). In this sensor the specific glucose binding reagent concanavalin A is immobilised to the inner wall of a hollow dialysis fibre tube. Within the tube fluorescein-labelled dextran competes for binding to the con A with glucose which diffuses through the dialysis fibre. Displaced labelled dextran is then detected by excitation and fluorescence emission measurement with fibres attached to the tube. This sensor represents an equilibrium measurement which does not require continuous mass transfer of glucose, and the sensor output is therefore less susceptible to changes in the membrane characteristics.

4.3 *Tissue sensors*

There are two important reasons why sensors for measurement in tissue have been considered and developed. First, it is considered to be less intrusive to insert microneedle sensors into the skin than to use intravascular devices. Furthermore, if sensors can be merely attached to the surface of the skin without penetration then this would be even more attractive and non-disturbing. Secondly, it is often the case that the physiological changes occurring in the periphery may provide an early indication of changes in the clinical condition of a patient, and this is due to the basic organisation of the body's interlocking control mechanisms which are designed to protect the vital organs at the expense of the more peripheral structures such as skin.

Of the species so far referred to, oxygen, carbon dioxide, pH and glucose (along with certain anaesthetic agents) have been measured with sensors inserted into cutaneous tissue or attached to the skin surface (Fig. 10).

The detection and treatment of shock in patients undergoing intensive care is important, and may be assisted through the use of microsensors for the continuous evaluation of peripheral perfusion. In shock, tissue perfusion is invariably reduced, leading to decreased cellular metabolism which will be reflected by changes in pO_2, pH, lactate and pyruvate. There are debates concerning the relative importance of each of these analytes, but there has been considerable interest in the development of microsensors for tissue pO_2 and pH measurement. Studies by KESSLER *et al.* (1976) showed that in haemorrhagic shock changes in the oxygen supply to skeletal muscle occur before deterioration is seen in arterial and venous pressure and arterial pO_2. A multicathode surface electrode was developed and reported by KESSLER and LÜBBERS, (1966), and this has been used by several groups to monitor and study organ surface pO_2. KOPP *et al.* (1981), used the multicathode electrode to monitor muscle surface pO_2 in critically ill patients, reporting its correlation to cardiac output and arterial pO_2. FONTIJNE *et al.* (1981) also used the multicathode sensor to assess the effects on microcirculation of either bubble oxygenators or membrane oxygenators for extracorporeal circulation. Other groups, such as DE KÖNING and VAN DER KLEIJ (1980) have used a pO_2 stab electrode, comprising of a 50 μm platinum wire encapsulated in glass and fixed into the tip of a 0·5 mm diameter stainless-steel needle. The authors report that measurement of pO_2 in skeletal muscle with such an electrode is a sensitive method for the early recognition of shock. GROTE *et al.* (1981) have used an arrangement comprising eight 15 μm diameter cathodes within a PTFE membrane covered assembly to measure brain surface pO_2. HUTCHINGS *et al.* (1988) have shown that it is possible to fabricate flexible thin-film O_2 sensors which may be used for measurements within wounds.

When using multiple cathode sensors or single cathode devices for monitoring or investigating microcirculatory pO_2, there is an advantage in presenting the data as a pO_2 histogram (KESSLER, 1967).

Tissue pH measurement has mainly been pursued with the use of glass microelectrodes. There has been particular interest in the use of tissue pH monitoring in the foetus during delivery. A pH electrode for subcutaneous measurement in the foetal scalp was first described by STAMM *et al.* (1974). The pH-sensitive tip is 1·3 mm in diameter and 1·00 mm in length, and the reference electrode and liquid/liquid junction surrounds the active part of the electrode. Although the glass pH electrode has provided useful infor-ation on foetal scalp pH changes, the method of application is not straightforward and the glass electrode is relatively fragile. Furthermore, the validity of using foetal scalp blood gas and pH measurements to assess foetal status has been brought into question, due to the possibility of scalp perfusion being reduced during contractions and subsequently invalidating scalp measurements.

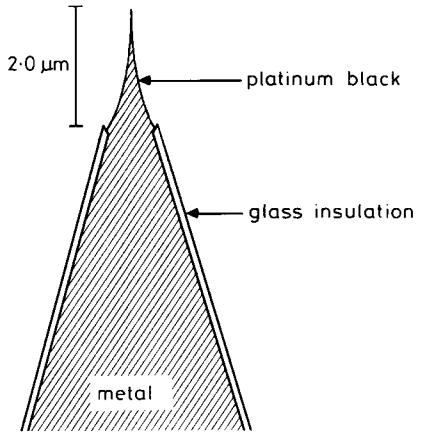

Fig. 10 *A microelectrode suitable for intracellular and extracellular measurements*

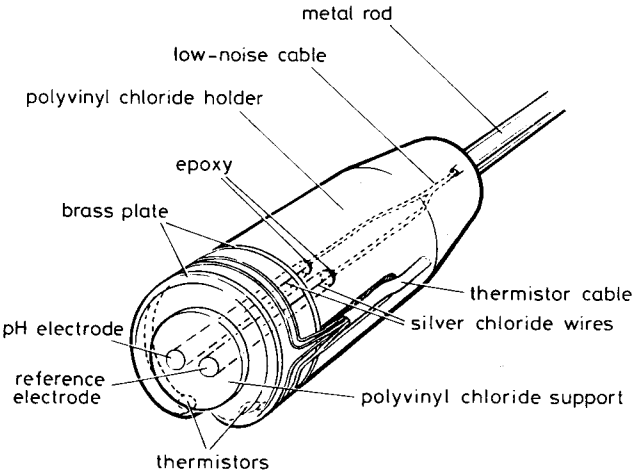

Fig. 11 *An electrically heated micro-pH electrode, for analysis of foetal scalp blood. (From O'DOWD et al. (1988) with permission)*

Foetal scalp blood sampling together with laboratory blood analysis still forms an imporant part of foetal assessment. To improve the practicalities of this method O'DOWD *et al.* (1988) have described a miniature pH sensor contained within an electrical heater which is designed to perform an analysis on a single drop of blood taken directly from the foetal scalp. Although both electrochemical and optical pH sensors may be used with this concept, O'DOWD *et al.* described the use of a polymer membrane-based potentiometric sensor (Fig. 11).

There has been considerable interest in developing glucose sensors for tissue measurement (KESSLER *et al.*, 1984; SHICHIRI *et al.*, 1982), in addition to the intravascular devices described above. Once again, the sensor is based on enzyme principles, with gold or platinum working electrodes combined with silver/silver chloride or stainless-

steel reference electrodes used for measurement of hydrogen peroxide resulting from the glucose oxidase catalysed oxidation of glucose. Measurements of glucose made with such sensors in subcutaneous tissue exhibit a significant quantitative difference as compared with blood determinations. Nevertheless, useful correlations appear to exist between tissue and blood measurements, although the limitations of such correlation need to be determined with further detailed clinical evaluations.

Early work on the measurement of oxygen at the skin surface (EVANS and NAYLOR, 1967*a*; *b*) subsequently led to the development of heated oxygen electrodes to be attached to the skin surface for the estimation of arterial pO_2 (HUCH *et al.* 1979; EBERHARD *et al.*, 1973; EBERHARD and MINDT, 1977). When the skin surface is heated to approximately 42°C, the cutaneous circulation is maximally vasodilated, and under these conditions the skin surface gas partial pressure correlates closely with arterial levels. Electrochemical oxygen sensors may be used for this purpose, and the method may also be used for measurement of other gases, particularly CO_2, but also N_2 and N_2O. So-called transcutaneous gas monitoring is used widely in neonatal intensive care, the relatively thin neonatal skin allowing good correlation. In adults the skin surface measurements are systematically different to arterial levels, with skin surface pO_2 being approximately 10 per cent lower than arterial pO_2. The method has also been used for foetal monitoring, with both electrochemical sensors (HUCH *et al.*, 1977) and also with mass spectrometry (ROLFE *et al.*, 1982).

Cutaneous blood flow is an important factor in determining the relationship between the skin surface and arterial gas levels. The method must therefore be used carefully in patients undergoing intensive care who may be in shock, because the skin surface gas levels will bear no sensible relationship with arterial values. Also, the method cannot provide reliable information in patients undergoing cardiac surgery with hypothermia.

The noninvasive nature of transcutaneous gas monitoring is an important advantage in clinical practice, and two further techniques, both based on optical principles, are also applicable. The first of these is pulse oximetry, in which optical absorbance changes at two wavelengths, due to arterial in-flow in a digit, are used to calculate oxygen saturation (YOSHIYA and SHIMADA, 1983). This method is now widely used for neonatal, paediatric and adult intensive-care monitoring, but the plethora of commerical instruments does require clinical users to ensure that they appreciate the characteristics of the particular system they use. The limit of accuracy with pulse oximeters is approximately 2 per cent, and this means that at high levels of oxygenation, where the S-shaped haemoglobin dissociation curve is flat, the corresponding range of pO_2 may be as much as tens of mm Hg. This may be a particular problem in pre-term babies who are susceptible to high levels of arterial oxygenation which can cause blindness. Pulse oximetry does not function in critically ill patients with poor peripheral circulation, but this may be detected by examination of the pulsatile absorbance signal.

Visible parts of the EM spectrum are highly absorbed by biological tissues, but in the near-infra-red absorbance is significantly reduced. This was recognised by JOBSIS *et al.* (1977), who suggested that cerebral oxygen utilisation could be monitored noninvasively with near-infra-red spectroscopy. REA *et al.* (1985*a*) proposed the use of this method for continuous monitoring of neonatal cerebral oxygenation, with a low-cost instrument containing four laser diodes as radiation sources and a silicon detector. Application of the Beer-Lambert law, which may not be strictly valid, allows calculation of the concentrations of the main absorbers: oxyhaemoglobin, deoxyhaemoglobin and the redox state of the key respiratory enzyme, cytochrome aa_3. This enzyme resides inside the mitochondria within cells, and it catalyses 95 per cent of the energy produced by aerobic metabolism. Near-infra-red spectrosopy may have an important place in adult, neonatal, and even foetal monitoring in the future, but more research is needed to resolve the outstanding theoretical problems presented by complex photon scattering phenomena in biological tissue (WICKRAMASINGHE *et al.*, 1989).

4.4 *Ex vivo systems*

There are several situations in which it is possible to gain access to a patient's vascular system and thereby to position sensors outside the body but in direct contact with blood. Examples of this are in open-heart surgery where patients are connected to an extracorporeal oxygenator, and in renal dialysis. In 1962 CLARK and LYONS described an extracorporeal electrode system for monitoring O_2 and CO_2 during cardiovascular surgery. Monitoring of newborn babies has also been carried out with external electrodes analysising 300 μl blood samples removed intermittently (every six and a half minutes) from an umbilical arterial catheter (VEASY *et al.*, 1971). With both of these systems the arterial blood removed from the patient is discarded after the measurement, and this simplifies the problem of the sterility of the system.

JANK *et al.* (1981) have described a shunt, called a 'Polyphore', which is moulded in silicone rubber and can accommodate five electrodes. This acts as an arteriovenous shunt, carrying blood at approximately 190 ml min^{-1} for the measurement of pH, temperature, oxygen saturation and pO_2. A similar system has been described by Osswald (OSSWALD *et al.*, 1977; OSSWALD, 1981), and this has been used for the measurement of potassium, calcium, pH and sodium, although with this system the blood sample is discarded after measurement. This has been used satisfactorily for the measurement of K^+ ions during open-heart surgery. A quad CHEMFET device has been described by SIBBALD *et al.* (1984), and this may be used for the *ex vivo* monitoring of K^+, Na^+, Ca^{2+} and pH.

5 Clinical considerations

The success or failure of *in vivo* sensors for chemical monitoring in intensive care depends upon a number of inter-related factors. It has been very common for the initial description of research results to be optimistic, even if these have been derived from *in vivo* animal studies. However, very few sensors have gone on to be accepted, even partially, for routine clinical use. The cost of *in vivo* sensors, which must necessarily be single-use disposable, has sometimes been referred to as an obstacle to routine use, but there is no evidence that this is really the case. It is therefore more likely, and perhaps more understandable, that failure to gain clinical acceptance is due to inadequate overall performance. It is very clear to anyone who has observed the rigours of a busy intensive-care unit that instrumentation and sensors must first, be straightforward to use, secondly must provide reliable information for diagnosis in therapy (Fig. 12), and thirdly must be safe. If these criteria can be met then the use of the technique will undoutedly aid patient care, and the cost will then be weighed against clinical benefits.

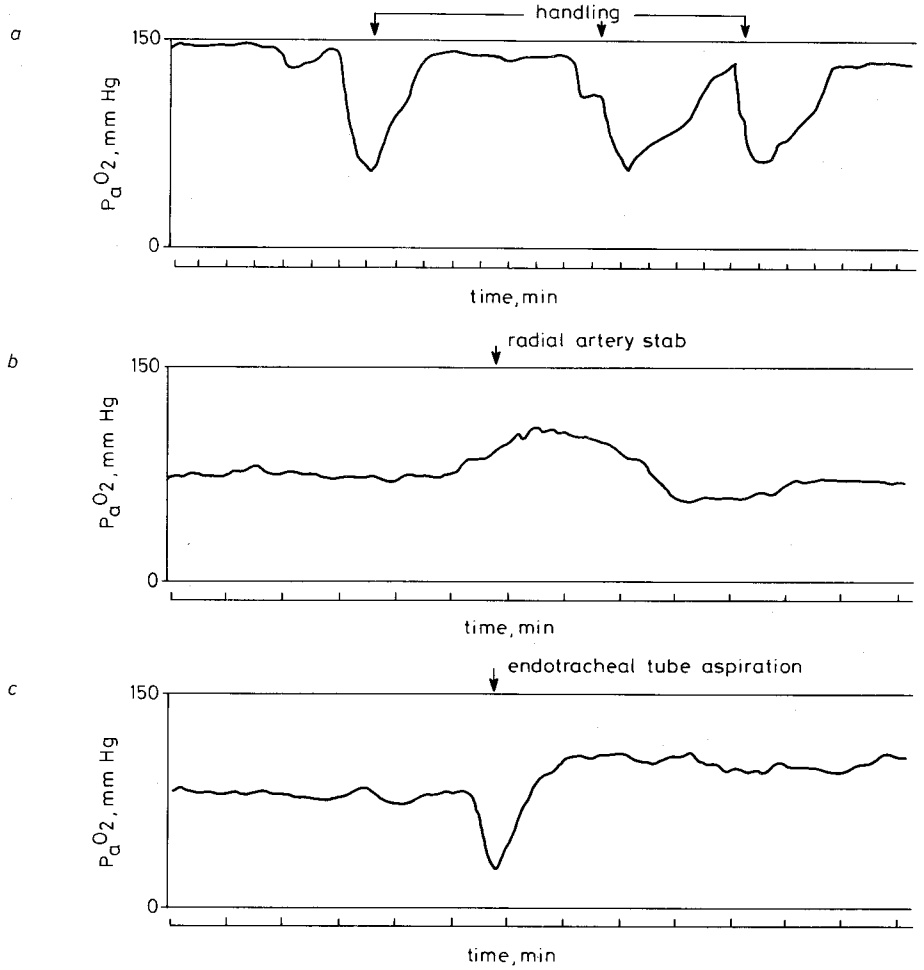

Fig. 12 *Arterial catheter pO_2 sensors may be used for continuous monitoring in neonatal intensive care (From* ROLFE *(1988) with permission)*

5.1 *Sterilisation*

A major constraint in sensor design is that the device should not introduce infection, and its design must therefore allow a satisfactory method of sterilisation to be carried out. The main methods of sterilisation which are relevant here are cold chemical sterilisation, autoclave, ethylene oxide and gamma irradiation. Ideally, sensors should be sterilised, and then packed ready for immediate clinical use.

Sensors for monitoring in the airway are relatively large, rugged, and reusable. Electrochemical or optical sensors for attachment to ventilator tubing may usually be adequately sterilised by cleaning with an alcohol swab. In some cases immersion in a cold liquid sterilent, e.g. glutaraldehyde, may be necessary. It will be apparent from Section 4.1 above that airway monitoring is sometimes carried out with an aspirating tube fixed in the airway or connections, together with a remote instrument, and in this case the connecting tubing may be single-use disposable.

Sensors employed for intravascular, invasive tissue measurement and *ex vivo* use present the most difficult problems regarding sterilisation. Of the available methods, that of gamma irradiation at 2·5 Mrad appears to have been the most successful, because it allows sensors to be packaged, stored and then used almost immediately clinically (GODDARD *et al.*, 1972; 1974; DODD, 1975; CONWAY *et al.*, 1976). Some polymers will deteriorate at high radiation doses, but single sterilisation at 2·5 Mrad does not adversely affect PVC, polyurethane, polyethelene, PTFE and rubber-modified polystyrene. Cold chemical sterilisation has been used for intra-arterial oxygen sensors (JANSEN *et al.*, 1978) the sterilent being 0·5 per cent chlorohexidine in water. The use of ethylene oxide at 40°C for 24 h achieves adequate sterilisation, but the procedure must be carried out carefully to ensure that outgassing has been completed before the device is used.

Despite the importance of the sterilisation of sensors, many articles have been published describing the human use of intravascular sensors but without mention whether or not sterilisation was carried out (LIM *et al.*, 1983). Similarly, a number of the *ex vivo* systems used in humans have been described with no mention of sterility (JANK *et al.*, 1981; RAMSING and RUZICKA, 1981; OSSWALD, 1981). Tissue electrodes for oxygen and pH measurement have also been described, once again without any details provided of sterilisation (DE KÖNING and VAN DER KLEIJ, 1980; ALEXANDER *et al.*, 1980 HENNER, 1980). Skin surface or transcutaneous gas sensors present fewer problems regarding sterilisation, but nevertheless it is importat that the sensors are cleaned with an alcohol swab, and with many sensor designs a disposable attachment ring is also used.

5.2 *Calibration and stability*

Gas sensors used for airway monitoring are relatively straightforward to calibrate, often with atmospheric air and perhaps a certified gas for zero or full scale reading. All systems used require periodic calibration checks, varying from once every few hours to once every 24 h. In addition, there are no practical difficulties concerning disconnection of the sensor or aspirating tube for calibration during use.

Sensors used for intravascular, invasive tissue and *ex vivo* monitoring may be calibrated immediately before and after use, as well as periodically during use. This is achieved by removing a blood sample, measuring the

appropriate chemical variable with a laboratory analyser, and subsequently calibrating the sensor against this reading. With this approach the sensors should remain stable with a tolerance of perhaps ±5 per cent from one calibration check to the next, and so the drift of calibration acceptable will be determined by the frequency of blood sampling. In neonatal intensive care, for example, arterial samples may be withdrawn every three or four hours, and drifts of 10–20 mm Hg over this period have been found (ROLFE, 1976). This puts a less stringent demand on sensor stability than, say, tissue glucose sensors designed to drift by no more than 5 per cent within a 24 h period. The tissue pH electrode developed by STAMM *et al.* (1974) is calibrated in sterile phosphate buffers at 37°C before use and studies have been reported in which the electrode is used for periods of up to several hours during labour and delivery with reasonable stability.

The effective operational lifetime of a sensor must also be determined by the particular application. Measurement of mixed venous oxygen saturation with a fibreoptic catheter oximeter may be carried out as an acute procedure taking a matter of tens of minutes. On the other hand, some patients may be under intensive care for days or even weeks, and clearly sensor lifetime must then be extended accordingly. Overall, however, sensors for intensive-care monitoring are most likely to be used for periods of one or two days, and this should be a target to be aimed for with most sensor designs.

5.3 *Biocompatibility*

The sensors used for invasive and *ex vivo* measurement are subject to deterioration due to undesirable interactions with the biological fluid with which they are in contact, i.e. blood, wound exudate, interstitial fluid. Sensor performance may be adversely affected as a result of membrane coating with proteins, cells etc., and the patient may be subjected to hazards from reactions initiated by the implantation of the sensor, such as blood coagulation, complement activation or inflammatory response.

The most difficult, potentially the most hazardous, problems clearly relate to the use of intravascular sensors, because poor haemocompatability of the sensor could lead to thrombus formation, following the processes of protein adsorption, platelet adhesion, platelet aggregation, fibrin formation and clot formation. The propensity of sensor surfaces to stimulate these interactions is influenced by physical phenomena such as surface roughness, as well as chemical factors such as the wettability and surface charge (SHARMA, 1981). The zeta potential is influenced by the extent to which certain charged groups are exposed or concealed at the surface, and platelets, erythrocytes, and vascular endothelium exhibit a negative surface charge in the region of −12 to −15 mV. The negative charges serve to generate repulsive forces between these constituents. This is a very simplistic description, because it is known that there is a distribution of charge over the surface of these biological materials, and variation can be both in magnitude and in polarity.

The anti-clotting agent heparin is frequently used, both when conventional catheters are inserted as well as when intravascular sensors are employed. Almost all workers who have described both animal and human use of intravascular and *ex vivo* devices have used heparin in some way. In animal preparations, the entire intravascular space may be heparinised. This approach is usually undesirable in critically ill patients, and therefore heparin may be confined to the infusion line of a catheter containing the sensor. It is also possible to bind heparin to the surface of catheters, and this has been reported to be beneficial in some cases (NILSSON *et al.*, 1981). The heparin coating was found to be stable and to prevent platelet adhesion and activation as well as activation of the plasma coagulation system (OLSSON *et al.*, 1977; 1980).

6 Conclusions

Research and development in the field of medical chemical sensors is continuing on a broad front, with the utilisation of electrochemical and optical principles attracting particular attention. While important basic research is being carried out to uncover new sensing principles for complex compounds, such as drugs and hormones, reliable *in vivo* sensors are still needed for a relatively small group of gases, ions, and catabolites for use in clinical medicine. Invasive sensors present the most difficult challenge, due to undesirable interactions between implanted sensor surfaces and the surrounding biological fluid, especially when the latter is blood. The solution to such problems may be derived from the utilisation of natural biological approaches to both sensing and intrinsic compatibility. At the same time, further development of noninvasive techniques, for example those employing near-infra-red spectroscopy, could provide useful means for the convenient monitoring of at least some clinically important chemical variables.

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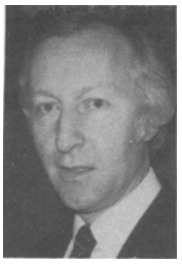
Authors' biography



Peter Rolfe gained his B.Sc. in Electrical Engineering, then, after a period in the aircraft industry, studied Physiology and was awarded a Ph.D. at the Royal Postgraduate Medical School, London. He established the Bioengineering Unit, and later the Biomedical Engineering Centre, at the University of Oxford and in 1987 was appointed to the Foundation Chair of Biomedical Engineering & Medical Physics at the University of Keele. Research interests include biosensors, electrical impedance tomography, in vivo near-infrared spectroscopy and technology for developing countries. He is Chairman of the UK Science & Engineering Research Council Committee on Medical Engineering and Sensors.

UK LINK programme in molecular sensors

Under the LINK initiative, set up by the UK government in 1986, matched funding from industry and government is targeted to encourage collaborative research. In September 1989, a £10 million 5-year LINK programme in molecular sensors was announced. Projects will be jointly funded by the UK Science & Engineering Research Council, the Department of Trade & Industry, the Agriculture & Food Research Council, the Department of Health and industry. Proposals, which must be submitted jointly by a research institute or academic group together with two or more companies, are assessed by a programme management committee.

The programme will focus on:

- selective sensors for metal and small molecular ions, and optical isomers
- immunoassay and enzymatic techniques to characterise biological and complex chemical systems
- guided wave optical and surface acoustic wave techniques
- sensors for non-destructive testing
- solid-state sensor devices and arrays which exploit microelectronic technology
- generic technology relating to ruggedisation, calibration, validation, manufacture and storage.

Further details from: Programme Coordinator, Dr John Free, 288 Croydon Road, Caterham, Surrey CR3 6QH, UK.

International Biosensors Society

A new international society to foster and focus activities in biosensors was formed following the First Annual Cambridge Conference on Commercial Applications of Biosensors, which took place in Cambridge, Massachusetts, USA, in February 1989. The objectives of the society relate very much to the activities of both manufacturers and users, and to academic and commercial developments. Spheres of interest already identified include applications in food processing, the pharmaceutical industry, and medical and environmental monitoring.

Further information from: Mr S. E. Skoug, One Kendall Square, Suite 250, PO Box 9171, Cambridge, MA 02139, USA.

Colloquium on Biosensors

4th-7th September 1990
Biochemical Society Meeting, Trinity College, Dublin. Contact: Wm Clayton Love, Biochemistry Department, Trinity College, Dublin 2, Ireland; tel: Dublin 772941.