Unless the catheter diameter approaches that of the vein, this change will be small and, in any case, is likely to be small compared with the upstream vascular resistance. Therefore insertion of the catheter is unlikely to change the volume flow rate of blood appreciably, although the local velocity profile may be substantially altered.

To some extent the mechanical effects of injection may be predicted theoretically. In the closed vascular system the primary effects upon flowing blood are a volume displacement and corresponding increase in system volume, and a small pressure increase. Validity of these predictions may be examined in model experiments.

However, in small diameter vessels with correspondingly low flow rates, the method of local thermal dilution is more susceptible to errors introduced by heat transfer from the extra-vascular thermal reservoir at 37° C.

REFERENCES

BARCROFT, H., and SWAN, H. J. C. (1953) *Sympathetic Control of Human Blood Vessels.* London, Arnold.
CLARKE, R. S. J., and HELLON, R. F. (1957) *Clin. Sci.* **16,** 103.
DOWSETT, D. J., and LOWE, R. D. (1964) *J. Physiol,* **172,** 13.
FRIEDMAN, S. M., JAMIESON, J. D., HINKE, J. A. M., and FRIEDMAN, C. L. (1959) *Amer. J. Physiol.* **196,** 1049.
FRONEK, A., and GANZ, V. (1960) *Circul. Res.* **8,** 175.
GREENFIELD, A. D. M., WHITNEY, R. J., and MOWBRAY, F. J. (1963) *Brit. med. Bull.* **19** . 101.
HINKE, J. A. M. (1959) *Nature,* **184,** 1257.
KETY, S. S. (1948) *Amer. J. med. Sci.* **215,** 352.
———— (1949) *Amer. Heart J.* **38,** 321.
MCGIRR, E. M. (1952) *Brit. med. Bull.* **8,** 192.
MORRIS, N., OSBORN, S. B., WRIGHT, H. PAYLING, and HART, A. (1956) *Lancet,* **2,** 481.
MOWBRAY, J. F. (1959) *J. appl. Physiol.* **14,** 647.
OSBORN, S. B., and WRIGHT, H. PAYLING (1949) *Brit. J. Radiol.* **22,** 110.
QUIMBY, E. H., and SMITH, B. C. (1944) *Science,* **100,** 175.
SMITH, B. C., and QUIMBY, E. H. (1944) *Surg. Gynec. Obstet.* **79,** 142.
SMYTH, C. N. (1965) *Med. Electron. biol. Eng.* **3,** 65.
SNODGRASS, C. A. (1965) Personal communication.
WHITNEY, R. J. (1949) *J. Physiol.* **109,** 5P.
———— (1953) *J. Physiol.* **121,** 1.
WRIGHT, H. Payling (1952) *Brit. med. Bull.* **8,** 187.

OXYGEN MEASUREMENTS IN BLOOD AND TISSUE

by

Professor J. P. Payne, M.B., F.F.A.R.C.S.

Department of Anaesthetics, Royal College of Surgeons of England

THE OBSERVATION BY Fernet (1857) that blood exposed to air contained a greater amount of oxygen than could be accounted for by simple solution was a crucial step in the recognition of the processes by which oxygen reaches the tissues from the atmosphere. Fernet postulated that oxygen

combined chemically with a constituent of the blood identified some years later by Hoppe-Seyler (1864) as haemoglobin. The relationship between oxygen and haemoglobin was established quantitatively by Hüfner (1890) when he showed that 1 gram of haemoglobin would combine with 1.34 ml. of oxygen. Since 100 ml. of normal healthy adult blood contains approximately 15 grams of haemoglobin this means that, when fully saturated, 100 ml. blood can carry in combination more than 20 ml. of oxygen which contrasts markedly with the 0.3 ml. held in solution by the same volume of blood. This small quantity in solution, however, is not unimportant; it normally reflects the oxygen tension in the alveoli from which oxygen is

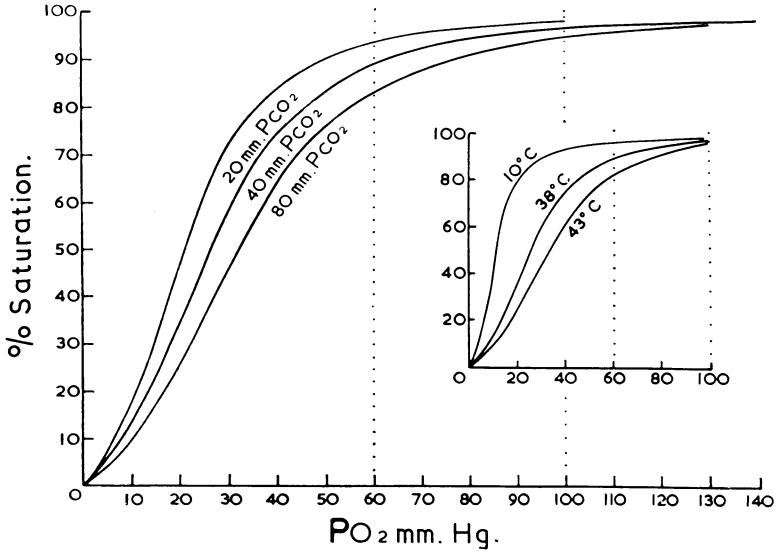

Fig. 1. The relationship between oxygen tension and saturation showing the influence of temperature and carbon dioxide on the slope of the dissociation curve (modified from Samson Wright's *Applied Physiology*, p. 168, 11th ed.)

absorbed and is a function of the tension available for supplying the haemoglobin and the tissues.

Under normal circumstances the oxygen tension of approximately 160 mm. Hg in the inspired air is reduced by dilution with water vapour and carbon dioxide to about 100 mm. Hg in the alveoli.

The relationship between oxygen tension and association with haemoglobin is not linear but follows an **S**-shaped pattern as shown in the oxygen dissociation curve (Fig. 1). Two points stand out when this curve is examined in detail. First, there is no significant increase in the amount of oxygen carried by the haemoglobin of the blood in the normal individual when the alveolar oxygen tension is raised above 100 mm. Hg and, second,

when the oxygen tension of the blood falls below 60 mm. Hg the oxygen dissociation from haemoglobin is greatly accelerated. This is the mechanism by which oxygen is made available to the tissues. Such availability is further increased by a fall in pH, a rise in temperature and an accumulation of carbon dioxide.

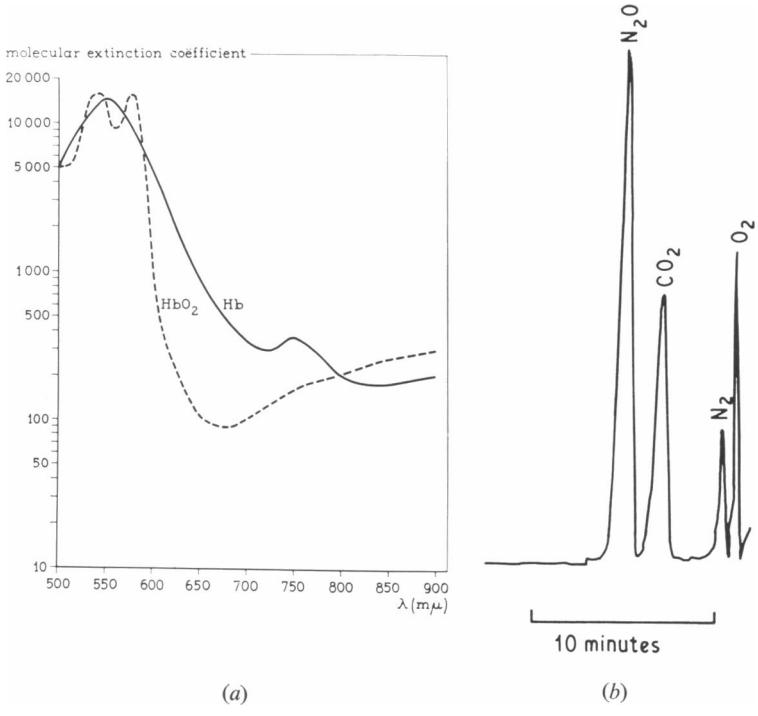

Fig. 2. (*a*) Graph showing the difference between the molecular extinction co-efficients of oxyhaemoglobin and reduced haemoglobin in the red region of the spectrum around 650 nanometres. In the infra-red range around 800 nanometres these co-efficients are equal. The optical absorption co-efficient can be expressed as a function of the molecular extinction co-efficient (from Reichert, 1965, in *Oxygen measurement in blood and tissue and their significance.* In press). (*b*) Typical gas chromatogram showing the discrete separation of the gaseous components in a blood sample. The chromatogram should be read from right to left.

It must now be clear that the transport of oxygen from the blood to the tissues depends fundamentally on the haemoglobin concentration and its degree of saturation with oxygen, the oxygen content of the blood and its oxygen tension. Fortunately, both from a clinical and a research aspect, accurate methods for measuring these parameters have been developed, although not all have reached that degree of refinement that allows them to be used routinely.

Measurement of oxygen saturation in blood

Methods of measuring oxygen saturation in the blood are based on the fact that there is a substantial difference in the optical absorption co-efficients of reduced haemoglobin and oxy-haemoglobin in the red region of the spectrum around 650 nanometres, whereas in the near infra-red range, around 800 nanometres, these co-efficients are equal (Fig. 2*a*). This simply means that reduced haemoglobin absorbs more red light than does oxy-haemoglobin, so that if a light beam is directed at a sample of blood the extent of the light absorption can be expressed as a function of the oxygen saturation.

Light which is not absorbed is scattered and, since both forward scattering (transmission) and backward scattering (reflection) can be measured, oximeters for measuring oxygen saturation fall naturally into two groups, transmission-type oximeters and reflection-type.

A transmission-type oximeter placed on the ear is commonly used for monitoring the degree of saturation during major surgery and a modification has been employed for the measurement of cardiac output by the dye dilution technique. Two main difficulties arise with this instrument. First, the blood flow through the ear must be arterialized and since this is usually done by producing a substantial increase in the flow without disturbing metabolism it may be difficult under certain circumstances such as stress, haemorrhage or cardio-vascular disease. Secondly, the transmission of red light depends not only on the degree of saturation but also on the quantity of blood present so that the blood flow rate through the oximeter must be maintained at a constant level. The ear oximeter has the advantage that no blood needs to be drawn and the disadvantage that the powerful light source commonly used may produce tissue damage. Calibration is often difficult and sometimes unsatisfactory in ill patients since it depends on full saturation being achieved by the inhalation of 100 per cent oxygen. In the upper range the ear oximeter has an accuracy of within 5 per cent, but the error increases to about 8 per cent at low saturation levels.

A reflection-type oximeter is used when the layer of blood or its conducting tube is too thick to allow light transmission, as, for example, when oxygen saturation in an artificial circulation is monitored. The instruments in routine laboratory use in this country are usually of the reflection type and one of the most popular is the haemoreflector described by Brinkman and Zijlstra (1949). This instrument has several advantages: no special training in its use is needed, the blood sample required for a single determination is small, 0.5 ml., and the analysis itself takes only a few minutes. The main disadvantage is that a calibration curve is needed for each patient and where widely varying changes are expected it is essential to repeat the calibration for every set of determinations.

Measurement of oxygen content of blood

Chemical and physical methods are usually combined for the determination of oxygen content. The standard reference method, that of Van Slyke and Neill (1924), gives a high standard of accuracy which, however, is critically dependent on the acquired skill of the operator (Linden *et al.*, 1965). Moreover, the relatively large blood volumes needed for duplicate analyses together with the time required for such analyses virtually preclude its use for multiple sampling, for example in children and most experimental animals. For these reasons the Natelsen (1951) modification of the basic technique has been found preferable in clinical laboratories.

An entirely new approach to the problem of blood gas analysis followed the introduction of gas chromatography. Chromatography can be defined most simply as a method for separating components in a mixture. Originally introduced as a means of recognizing unwanted constituents,

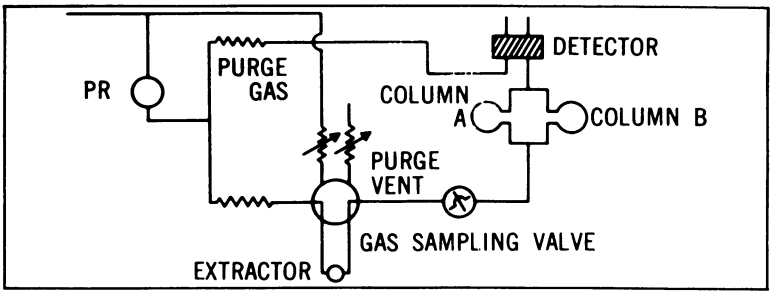

Fig. 3. Schematic diagram of a typical gas chromatograph. A pressure regulator (P.R.) controls the gas flow and parallel columns extend the range of separation.

refinements of technique have now made it possible not only to identify the various components of the mixture but also to measure their concentrations with a high degree of accuracy.

The technique is based on the observation that when different substances are passed through an inert material, such as silica gel, they become selectively adsorbed, their affinity being related to certain physical characteristics among which the boiling point is particularly significant.

In the typical blood gas chromatograph (Fig. 3) the inert material is packed into a heated column of small diameter metal tubing of varying length. This is the stationary phase through which the carrier gas or moving phase travels at a constant rate. When a sample is injected it is swept through the stationary phase by the carrier gas, for example hydrogen or helium, and its components become adsorbed in proportion to their affinity for the material, and ultimately emerge from the column in the inverse order of their affinity. By suitable detectors, such as thermal

conductivity cells, the components can be identified. As they pass through the detector a signal, varying in intensity with the strength of the individual components, is transmitted to a recorder which transcribes it in the form of a peak. The area under the peak is an accurate representation of the concentration. When, however, the peaks are symmetrical, sharply defined and narrowly based, the height itself is directly related to the concentration (Fig. 2*b*).

The fact that it is possible to use a gas chromatograph to analyse virtually all the components present in clinical mixtures of anaesthetic and respiratory gases has been known for some time. The analysis of gas mixtures presents no special difficulties and indeed the technique has been used for example to monitor the inspired concentrations of halothane and other anaesthetic vapours. But with blood gases the problem has been to ensure that the blood sample is completely purged of its gas content before analysis takes place. In practice, chemical extraction has proved effective, and in the Research Department of Anaesthetics in the Royal College of Surgeons Dr. Hill (1965) has recently shown that individual determinations of oxygen content by a gas chromatographic method agreed to within 2 per cent of simultaneously determined Van Slyke values. In his hands operator fatigue was not a problem even when 50 samples were analysed in one day.

For the anaesthetist the method has the added advantage that by the suitable choice of the stationary phase simultaneous determinations of nitrous oxide concentrations in blood can be obtained. With the description recently of a practical method for the calibration of such a chromatograph (Yee, 1965) the technique promises to be one of the most useful yet developed.

Measurement of oxygen tension in blood

Oxygen tension in blood and in tissues can be measured by polarography. This is a method of chemical analysis based on the fact that when an inert metal such as gold, mercury or platinum is negatively charged and immersed in an electrolyte it will give up electrons to dissolved oxygen. The transfer of electrons is proportional to the current flowing which in turn depends on the oxygen concentration. The resultant voltage change is measured and expressed in terms of oxygen tension.

The first measurements of oxygen tension in blood by polarography were carried out with a dropping mercury electrode, but this proved both tedious and difficult to use. Thus when Clark (1956) demonstrated that it was possible to separate the entire electrical cell from the blood by means of a thin polyethylene membrane which prevented the passage of electrolytes but remained permeable to oxygen a new stage in the development of oxygen electrodes was begun.

Criteria for the use of Clark-type electrodes for the accurate determination of blood-oxygen tension have been defined by Severinghaus (1959) as follows: The temperature in the electrode environment should be kept constant to $\pm$ 0.1 C. degree, there should be no pressure change in the liquid, it should be possible to equilibrate the sample of blood with known gas tensions, oxygen should neither be added nor removed from the sample and, finally, it should be possible to stir the liquid in contact with the membrane at a constant velocity.

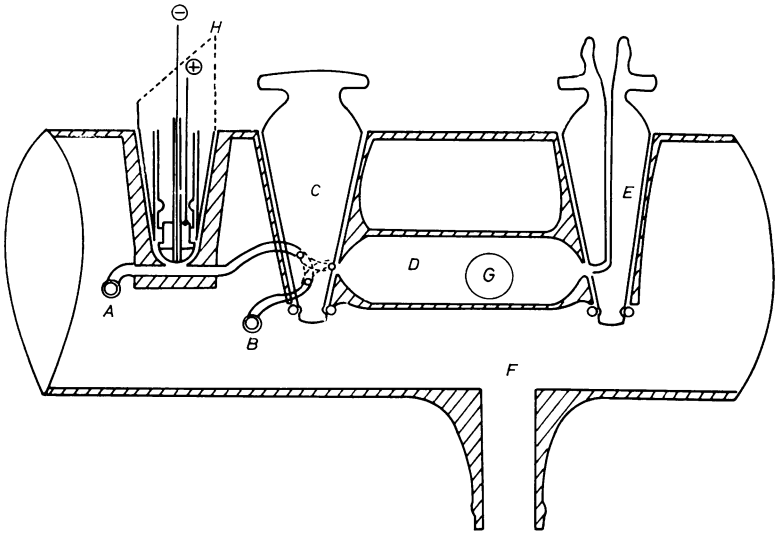

Fig. 4. Apparatus for measuring oxygen content and oxygen tension on the same blood sample. The apparatus is first filled with sodium ferricyanide solution and the oxygen tension of this solution is measured by the platinum electrode (H). Next the chamber (D) is closed by the stopcocks (C) and (E) and the capillary (A–B) filled with blood after removing the ferricyanide. The oxygen tension of the blood is measured after which the stopcocks are opened and 25µl. driven into the chamber by a microsyringe. The stopcocks are closed and the reaction started by agitation of the glass ball (G). After completion of the reaction the oxygen tension of the solution in (D) is measured. From the difference in oxygen tensions the oxygen content is calculated (from Lübbers, 1965, in *Oxygen measurement in blood and tissue and their significance*. In press).

The polarographic method of determining oxygen tension in blood has also been applied to the measurement of oxygen content. In 1940 Baumberger pointed out that if the chemically bound oxygen of haemoglobin were converted to physically dissolved oxygen the proportional increase in tension could be measured and expressed in terms of content. More recently Linden *et al.* (1965) have described a simple method for the determination of oxygen and carbon dioxide content in blood which depends on polarographic measurement, and a particularly elegant micromethod has been developed by Fabel and Lübbers (1964) which enables

them to measure both oxygen tension and oxygen content in a 25 microlitre sample of blood in five minutes (Fig. 4). It should, however, be emphasized that commercially produced electrodes have not yet reached a

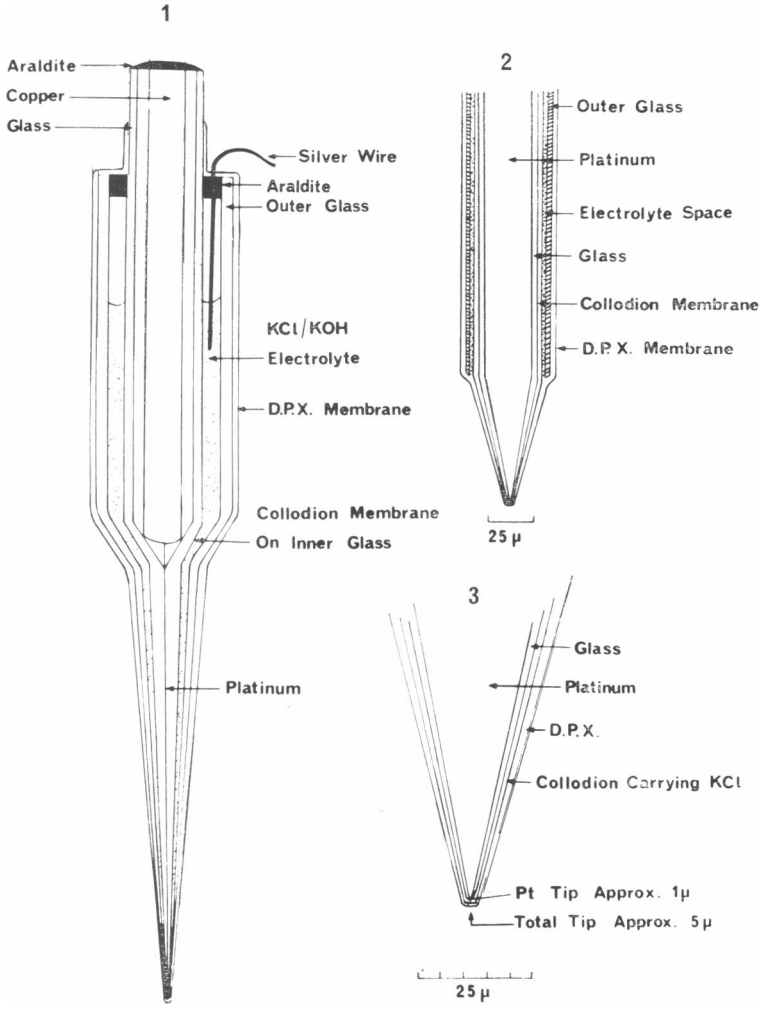

Fig. 5. Details of design of tissue probe electrodes described by Silver, 1965, in *Oxygen measurement in blood and tissue and their significance.* (In press)

standard which allows them to be used freely for research, although in clinical work, where the measurements are less critical, satisfactory results have been obtained.

Measurement of oxygen tension in tissues

Many attempts have been made to measure oxygen tension in tissues but until recently so unsuccessfully that there has been a tendency to rely on indirect data obtained for example by the analysis of air bubbles in-

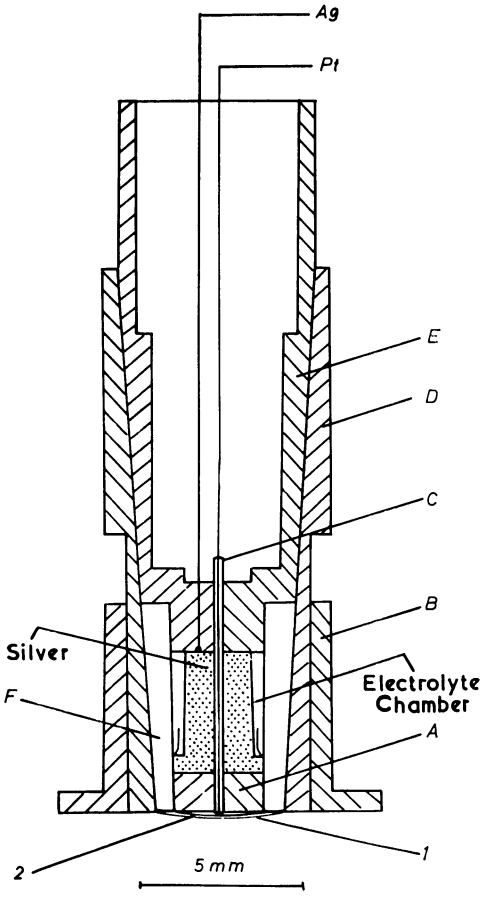

Fig. 6. Oxygen electrode for measuring oxygen tension at tissue surfaces. Details of construction and use in Kessler and Lübbers (1964) *Pflügers Arch. ges. Physiol.* **281,** 50.

jected into organs and allowed to equilibrate with the surrounding tissues. Alternatively, tissue-oxygen tensions have been deduced from a knowledge of arterio-venous oxygen differences and the oxygen tension in venous blood.

A full description of the problems involved in the measurement of oxygen tension in tissues has recently been provided by Silver (1965), who also

described a tissue probe developed from a design for a Clark-type microelectrode. This instrument, which works on the same principle as the large Clark electrode, has the advantage of a short response time and a tip-size no greater than 5 μ, which causes minimal tissue damage (Fig. 5). With such an electrode Silver has been able to demonstrate rhythmic fluctuations in oxygen tension in organs such as the brain and testis. These seem to follow two main patterns which are at present under investigation (Silver, 1965).

Apart from tissue probing, electrodes have been constructed for measuring oxygen tension on the surface of organs. The electrode shown in Figure 6 was designed by Kessler and Lübbers (1964) for measuring oxygen tension on the surface of the liver. Since it weighs only 800 mg. it can be supported by the tissue itself and is small enough not to interfere with the blood flow in the organ.

Significance of oxygen measurements

The primary object of oxygen measurements is to assess as accurately as possible the effectiveness of tissue oxygenation and for this purpose the oxygen availability needs to be known. The availability is simply the amount of oxygen transported to the tissues and is the product of the oxygen content of the arterial blood and the cardiac output (Richards, 1943–44). Normally the oxygen consumption is only 25 per cent of that transported, leaving a reserve of 75 per cent. Under certain circumstances, however, such as high altitude climbing or flying, haemorrhagic or other forms of shock or heart failure, the oxygen availability is reduced and the reserve may become critically low.

Richards's concept of oxygen availability can be expressed mathematically as follows:

$$\text{Available } O_2 = \underset{\text{output}}{\text{cardiac}} \times \underset{\text{concentration}}{\text{haemoglobin}} \times 1.34 \times \underset{\text{saturation}}{\text{percentage}}$$

It would appear from this equation, therefore, that if the haemoglobin concentration and the oxygen saturation are determined the oxygen content can be calculated and there is no need for either content or tension measurements. It has even been suggested that the determination of the arterial oxygen tension is simply an elegant way of measuring content and that oxygen tension in itself has no particular value. Such a suggestion betrays a fundamental lack of understanding of the factors involved in oxygen transport. It cannot be emphasized too strongly that oxygen *tension* as distinct from oxygen *content* is essential to life. The transport of oxygen from capillaries to the mitochondria is dependent on an adequate tension gradient. A large amount of oxygen dissolved in the blood will not maintain cellular oxygenation if the tension is too low, but even a small amount in solution will be adequate if the tension is high enough. Thus the driving force which carries oxygen from one tissue to another is its *tension*.

This can be explained on the basis of the oxygen solubility co-efficient. The amount of oxygen dissolved in any tissue is dependent on the corresponding co-efficient which varies from tissue to tissue so that for a given oxygen tension different tissues have different contents; under these circumstances it is perfectly possible for oxygen to move from a tissue of low content to one of high content. Content *per se* therefore plays little part in supplying the tissues' oxygen needs.

At the cellular and subcellular level oxygen tension is equally important. This importance is not confined to its metabolic role in the respiratory

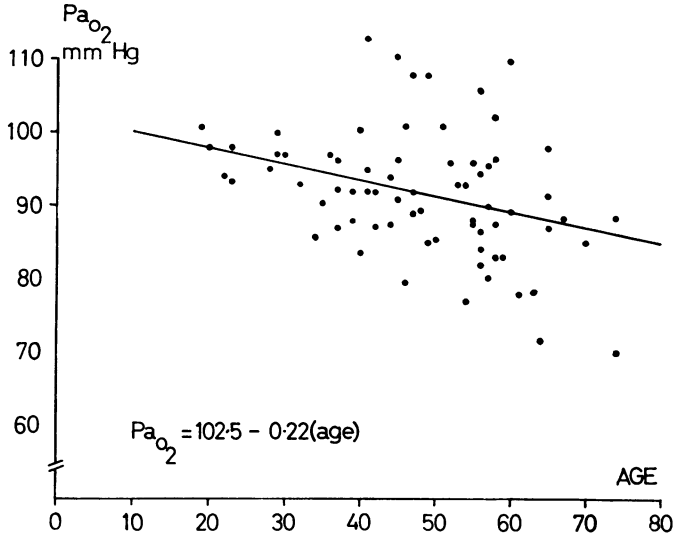

Fig. 7. Graph of arterial oxygen tensions plotted in relation to age. The points represent duplicate estimations of arterial oxygen tensions in 70 adult patients. The regression line and the formula from which it was derived are shown. (From Conway, Payne and Tomlin, 1965, *Brit. J. Anaesth.* **37**, 405.)

electron transport system. It is now well established that many enzymes are most effective within a relatively narrow range of oxygen tension; those involved in the oxidation of pyruvate fall into this category and many mitrochondrial oxidative pathways are inhibited by oxygen lack (*Lancet*, 1965*a*).

Measurements of arterial oxygen tension have also a practical value. Because of the shape of the haemoglobin-oxygen dissociation curve very small changes in saturation correspond to relatively large changes of tension at the upper end of the curve in patients breathing air. Consequently oxygen-tension determinations provide a more sensitive means of detecting mild hypoxaemia than saturation measurements.

This has been clearly demonstrated by work on post-operative hypoxaemia during the past few years reviewed recently in a leading article in the *Lancet* (1965*b*.) In 1962 Nunn and Payne demonstrated that hypoxaemia was a frequent occurrence in the immediate post-operative period after even the most trivial surgery under anaesthesia, and the many papers that have followed, exploring and amplifying the original observations, have been dependent largely on the ability to measure oxygen tension precisely.

In turn, this has raised again the question of the normal range of oxygen tensions in surgical patients and some authors, notably Stephen and Talton (1964), have argued that this is still unknown. However, Conway *et al.* (1965) have shown that there is a marked inverse relationship between oxygen tension and age in such patients when those with clinical cardiovascular and respiratory disease are excluded. From their determinations of arterial oxygen tensions in 70 patients awaiting surgery a regression coefficient of $PaO_2 = 102.5 - 0.22$ (age) with a standard deviation of 4.7 mm. Hg was derived (Fig. 7). This is in reasonable agreement with the equation of Raine and Bishop (1963), who calculated that $PaO_2 = 103.7 - 0.24$ (age) mm. Hg in 49 healthy volunteers.

With the development of new methods of treatment both in surgery and in radiotherapy, and the greater availability of hyperbaric oxygen chambers, it has become critically important to have suitable means of measuring oxygen content and tension accurately. Since many such measurements will be carried out on small children and infants the need for suitable micro-methods is obvious. Fortunately some of the techniques described above can be adapted reasonably easily for clinical work and with the greater accuracy involved a corresponding improvement in the management of patients can be expected.

REFERENCES

BAUMBERGER, J. P. (1940) *Amer. J. Physiol.* **129,** 308.
BRINKMAN, R., and ZIJLSTRA, W. G. (1949) *Arch. Chir. Neerl.* **1,** 177.
CLARK, L. C. (1956) *Trans. Amer. Soc. art. Int. Org.* **2,** 41.
CONWAY, C. M., PAYNE, J. P., and TOMLIN, P. J. (1965) *Brit. J. Anaesth.* **37,** 405.
FABEL, H., and LÜBBERS, D. W. (1964) *Pflügers Arch. ges. Physiol.* **281,** 32.
FERNET (1857) cited by E. Neil in *Oxygen measurement in blood and tissue and their significance*, ed. Payne and Hill. London, Churchill. In press.
HILL, D. W. (1965) in *Oxygen measurement in blood and tissue and their significance*, ed. Payne and Hill. London, Churchill. In press.
HÜFNER, G. (1890) *Arch. Anat. Physiol.* **1.**
HOPPE-SEYLER, F. (1864) *Virchows Arch. ges. Phys.* **29,** 233.
KESSLER, M., and LÜBBERS, D. W. (1964) *Pflügers Arch. ges. Physiol.* **281,** 50.
Lancet (1965*a*) Leading article, **1,** 1105.
Lancet (1965*b*) Leading article, **1,** 1257.
LINDEN, R. J., LEDSOME, J. R., and NORMAN, J. (1965) *Brit. J. Anaesth.* **37,** 77.
NATELSEN, S. (1951) *Amer. J. clin. Path.* **21,** 1153.
NUNN, J. F., and PAYNE, J. P. (1962) *Lancet*, **2,** 631.
RAINE, J. M., and BISHOP, J. M. (1963) *J. appl. Physiol.* **18,** 284.
RICHARDS, D. W. (1943–44) *Harvey Lecture Series*, **39,** 217.

SEVERINGHAUS, J. W. (1959) in *Symposium on pH and blood gas measurement*, ed. R. F. Woolmer. London, Churchill.
SILVER, I. A. (1965) in *Oxygen measurement in blood and tissue and their significance*, ed. Payne and Hill. London, Churchill. In press.
STEPHEN, C. R., and TALTON, I. (1964) *Canad. Anaesth. Soc. J.* **11**, 586.
VAN SLYKE, D. D., and NEILL, J. M. (1924) *J. biol. Chem.* **61**, 523.
YEE, H. Y. (1965) *Analyt. Chem.* **37**, 924.

THE APPLICATION OF ELECTRONICS TO SURGERY

by

D. W. Hill, M.Sc., Ph.D., F.Inst.P., M.I.E.E.

Research Department of Anaesthetics, Royal College of Surgeons of England

NOWADAYS, IT SEEMS that almost anything can be done more easily and more rapidly with the aid of electronic techniques. The last decade has produced a great proliferation of medical electronic apparatus, and currently many doctors are thinking in terms of applying computer techniques to their work. It all seems very far removed from the Romans treating headaches with the shock from an electric eel, Galvani's "animal electricity" experiments, Emil Du-Bois Reymond winding three miles of wire for his galvanometer coil in order to obtain sufficient sensitivity for his work in electro-physiology, and Duchenne's lifetime of work on the treatment of patients by the application of static electricity. It is indeed gratifying to see how physiologists make use of each new technical advance produced by electrical engineers, and this leads to the wide range of medical electronic equipment available to surgeons to-day.

A convenient start can be made by considering the use of electronic techniques pre-operatively. A simple instance occurs in the use of a transistorized electronic stethoscope, so that a group of students may simultaneously listen to the same heart sound as their instructor. More complicated diagnostic procedures are being made possible, or made more rapid, by the use of electronics. Cardiac catheterization is now a routine procedure, which has benefited by the use of X-ray image intensifiers for the location of the position of the catheter tip, and the availability of efficient electro-manometers for the recording of the blood pressures. The recording of cardiac outputs by the well-known dye dilution technique has been simplified by the development of compact cuvette densitometers based on semiconductor photo-cells, and the design of analogue computers to reduce the laborious calculations associated with the dye curves. If desired, it is now feasible to record serial cardiac outputs at one-minute intervals. Digital computer programmes have been written which will allow the computer to perform all the calculations associated with a detailed cardiac catheterization, such as those to determine cardiac output, cardiac index, appearance time for a dye curve, mean transit time, central