

[54] **OXYGEN OR CARBON MONOXIDE DETECTOR**

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; a part interest

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73/27 R, 73/194 E, 128/2 E, 324/29

[51] Int. Cl. **A61b 5/00**, G01n 27/42, G01n 33/16

[58] Field of Search 23/230 B, 253 R, 254 E;
324/29; 128/2 E, 26, 2.1 E, 2.05 D; 73/27 R,
194 E; 338/13, 20

[56] **References Cited**

UNITED STATES PATENTS

3,558,279 1/1971 McRae et al. 23/254 E
3,689,222 9/1972 McFarland et al. 23/253 R X

OTHER PUBLICATIONS

Diagnostic Biochemistry - Searcy pp. 270-278, Rec.
Patent Office Apr. 1972, Copyright 1969
McGraw-Hill, Inc.

An Encapsulated, Implantable Metal-Oxygen Cell as a
Long Term Power Source for Medical and Biological
Appl., Tseung et al., Med. & Bio. Engng. Vol. A, pp.

175-184, Pergamon Press, 1971, p. 176.

Thorpe, Dict. Dict. of Appl. Chemistry, Fourth Ed.,
Vol. II, p. 346.

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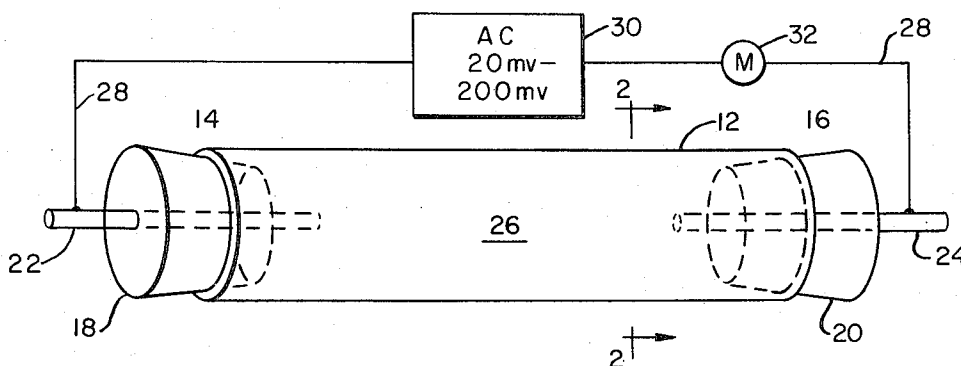
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Schurgin

[57]

ABSTRACT

An oxygen sensitive resistor for the detection of oxygen levels. The resistor includes an oxygen permeable membrane enclosing a reversible acting oxygen binding material. The oxygen binder absorbs oxygen diffusing across the membrane in a reversible process to vary the number of charge carriers between resistor electrodes and correspondingly change the resistance of the binding material as a function of bound oxygen. When used in vivo, the binding of oxygen in the resistor reaches an equilibrium representative of oxygen content of the tissues or blood external of the membrane so that accurate oxygen level measurements are not dependent on rates of oxygen diffusion through the membrane which are difficult to control. A similar gas binding effect is employed to provide a carbon monoxide detector.

16 Claims, 8 Drawing Figures



SHEET 1 OF 2

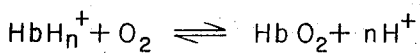
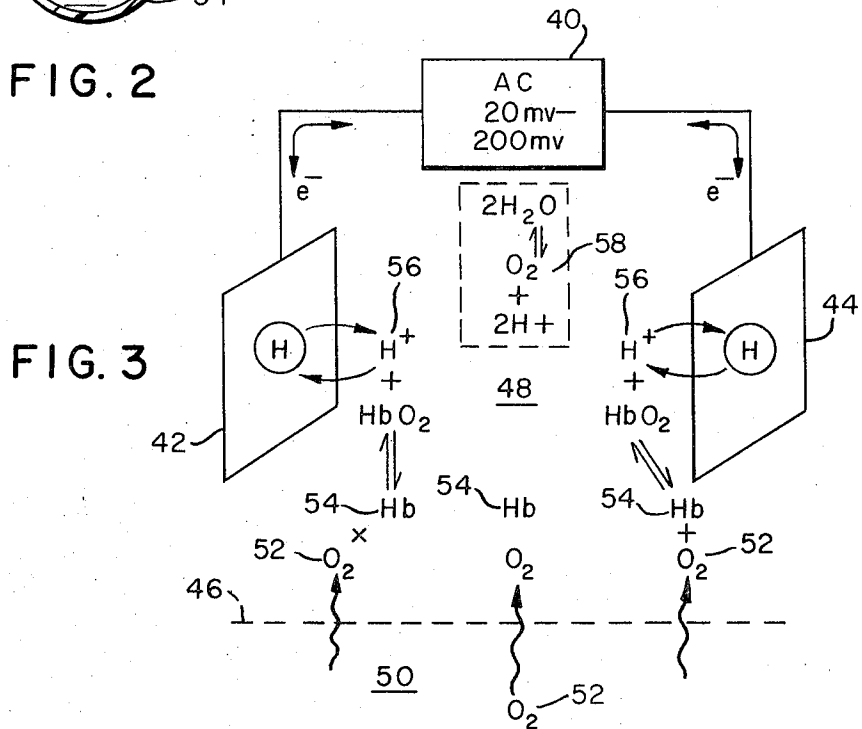
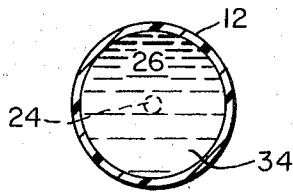
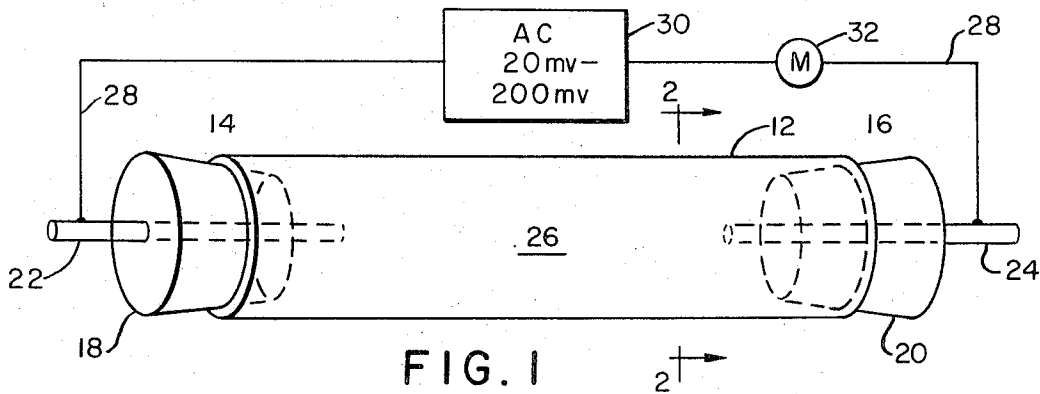


FIG. 4

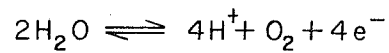
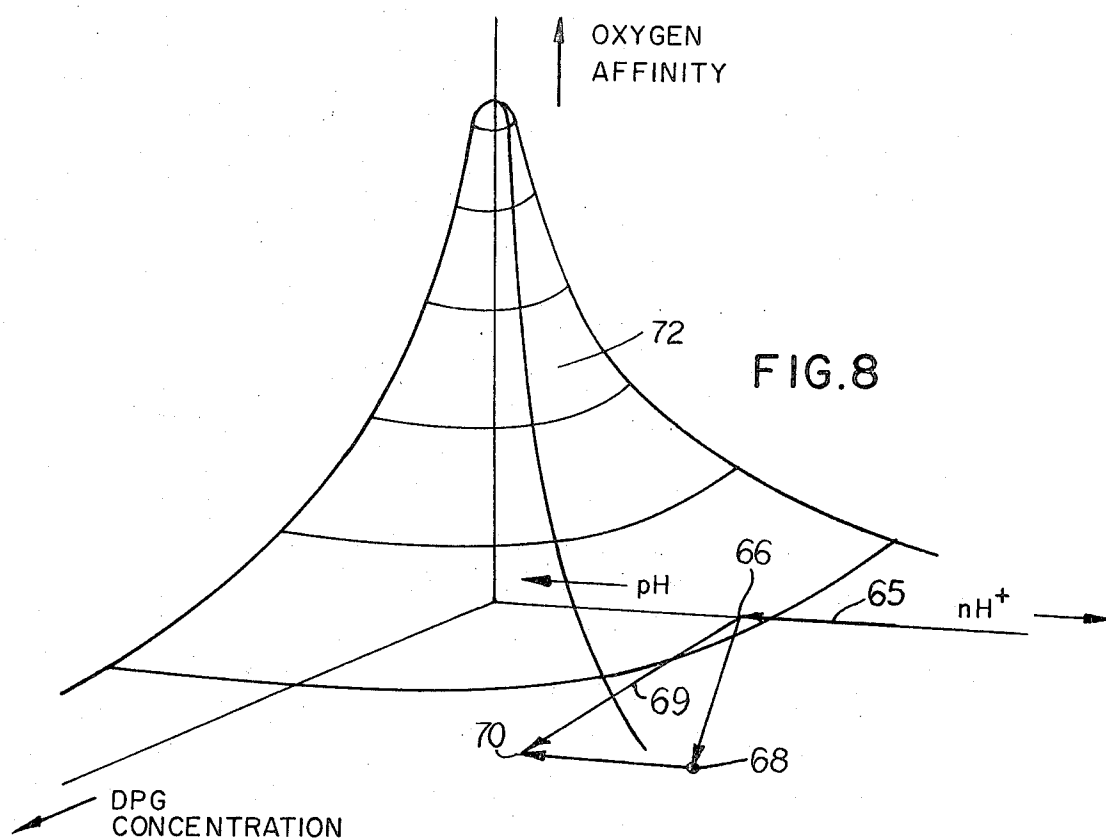
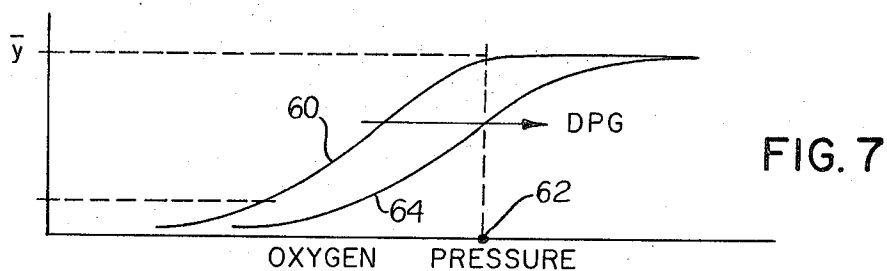
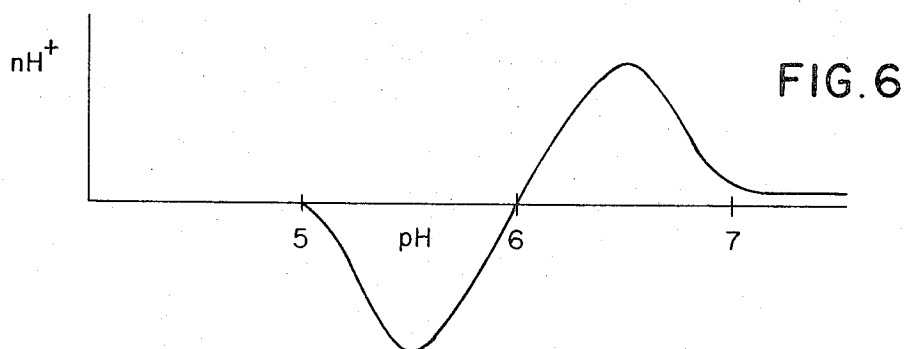


FIG. 5



OXYGEN OR CARBON MONOXIDE DETECTOR

FIELD OF THE INVENTION

This invention relates to condition responsive resistances and in particular to an oxygen sensitive resistor whose resistance varies in response to absorbed oxygen.

BACKGROUND OF THE INVENTION

Several important aspects of human medical conditions can be monitored or predicted by detection of the oxygen level of the blood and of other human tissues. As one example, cardiac arrest can be predicted by monitoring a lack of oxygen at the heart muscle. The condition of hyperoxia which manifests itself in too great an abundance of oxygen in the blood stream and fed to the tissues can lead to a number of disruptions in body processes including damage to the lungs, central nervous system and the optic system, and can be detected from oxygen level monitoring.

These and other conditions of tissue oxygen level are commonly monitored by detecting blood oxygen levels as an indication of oxygen available to the tissues. Many commonly used drugs, however, such as the anesthetic halothanes disrupt the process of transferring oxygen from the blood to the tissues so that blood oxygen level is not a reliable measure of oxygen which reaches the tissues. A direct measurement of tissue oxygen is thus often necessary to provide the desired indication.

Thus, in the many cases where it is desirable if not critical to employ in vivo monitoring of tissue and blood oxygen levels, particularly over extended periods of time, to predict or monitor patient conditions with a view toward preventive or curative treatment, an oxygen level detector is needed which is small in size, non-toxic, and adapted for long term accuracy. It is also desirable to have a detector respond relatively quickly to changing oxygen levels and to provide such a minimal consumption of oxygen as not to disrupt the oxygen level in the blood or tissue where monitoring is desired. While it is often preferable or necessary to measure oxygen content in vivo because of a desire not to affect or invade living blood or tissue by its removal, many of the features for an oxygen level detector are also desirable for in vitro measurement outside of the body.

Because of the importance of being able to detect blood oxygen levels and the complex requirements for a simple and reliable blood detector, many methods and devices have been developed to determine oxygen level; but none have been able to provide all of the desirable qualities discussed above. A particular significant defect of the implantable detectors is that in measuring the oxygen level they consume and destroy a certain amount of blood oxygen as part of their mechanism for detecting its concentration. This continuous oxygen consumption, coupled with a need to isolate the oxygen detector from the blood stream necessitates a flow of oxygen from the tissue monitored to the detector through some physical barrier by the process of diffusion. The rate of diffusion affects the level of oxygen available for consumption by the detector and correspondingly affects the indication of oxygen present in the tissue. Thus, the accuracy of prior art implantable oxygen detectors has been limited by a build up of fibrin and other proteins on the device which increases

the diffusion path and lowers the diffusion rate. Accordingly, these prior art devices have been limited in life times to several hours in vivo use. Additionally, this diffusion limitation of prior art detectors has made them sensitive to movement or position in the blood stream or tissue and has often required that an agitation or oscillation of the detector be employed to standardize its response.

Among the implantable devices suffering from these deficiencies are included the oxygen electrode, oxygen cathode, Clark electrode, lead anode, H₂ fuel cell, O₂ concentration cell, and the enzyme electrode. Also mass spectrometers and paramagnetic detectors located in vitro have been coupled through oxygen permeable membranes to provide monitoring of oxygen at desired body locations. These techniques are generally complicated, bulky or short lived in their usefulness. External oxygen level measurement has typically been provided by mass-spectrometers, manometric detectors, paramagnetic detectors or optical and ultra violet measurements which require the taking of a sample of the blood or body tissue. Such samples may not be from a desired location and there is a substantial time delay before an accurate indication of oxygen level is available. Many additional factors such as temperature, pH, and oxygen consumption by the tissue affect the accuracy of these in vitro techniques and they must be accounted for if useful oxygen level measurements are to be made.

BRIEF SUMMARY OF THE INVENTION

These and other desirable features for an oxygen level detector are provided in a preferred embodiment of the present invention comprising an encapsulated oxygen sensitive resistor which may be used in vitro and which is also readily implantable since it operates by oxygen absorption rather than consumption to avoid the problem of diffusion limitation.

The detector includes an efficient oxygen binding substance in an electrolyte solution. The solution is contained within an oxygen permeable membrane. Opposing electrodes are provided through the membrane to contact the electrolyte and oxygen binding material and the electrodes are excited with a low A.C. voltage. The oxygen binding material is selected to have the property of reversibly reacting with the oxygen to release charge carriers, such as protons, that in turn affect the conductivity of the material between the electrodes.

When the entire detector is placed in vivo either in the blood or the body tissue, oxygen diffuses across the membrane and is bound until an equilibrium condition is reached. The resistance of the solution between the electrodes is detected by the impedance to the flow of the alternating current excitation to provide an accurate indication of the concentration of oxygen in the neighborhood of the detector. At equilibrium there is little or no net diffusion of oxygen across the membrane so that the gradual formation of fibrin and other materials around the exterior of the membrane has no effect upon the accuracy of the reading but only increases somewhat the response time of the detector to changes in oxygen level.

Additional substances may be added to chemically bias the reversible oxygen binding reaction to a more efficient operating condition.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the present invention will be more clearly described below in a detailed description of the preferred embodiment presented for purposes of illustration, and not by way of limitation, and in the accompanying figures of which:

FIG. 1 is a diagrammatic view of the oxygen sensitive resistor according to the invention;

FIG. 2 is a cross-sectional presentation of the FIG. 1 view;

FIG. 3 is a diagram illustrating resistor operation;

FIGS. 4 and 5 are equations representing further operational characteristics of the invention; and

FIGS. 6, 7 and 8 are graphs useful in explaining the operation of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

With reference to FIG. 1 an oxygen sensitive resistor is shown operating on the principle of a reversible oxygen binding reaction rather than oxygen consumption so that diffusion rates in the oxygen exchange between the resistor and the environment affect only the time constant of the measurement rather than the absolute accuracy. In particular a cylindrical oxygen permeable sheath 12 is closed at opposing ends 14 and 16 with respective plugs 18 and 20. The plugs 18 and 20 have respective electrodes 22 and 24 therethrough into an interior cavity 26 of the sheath 12. An electrical conductor 28 connects the electrodes 22 in a series connection to a low voltage A.C. source 30 and ammeter 32, and closes the circuit by connection to the electrode 24. FIG. 2 shows a sectional view of the resistor along the section line perpendicular to the axis of cylindrical sheath 12 as indicated by the section lines in FIG. 1.

In the design of the preferred resistor the material forming the sheath 12 is formed from a 1 mm. thickness of medical grade dimethyl siloxane to provide a highly oxygen permeable diffusion membrane. Other materials with a good oxygen permeability, particularly if they have low permeabilities to other gases and materials, may be substituted. The dimensions of the cylinder 12 are not critical and may be tailored to the specific application or in vivo situs of the resistors use. Accordingly the resistor may be located in the body blood stream or positioned in tissues such as the cardiac wall to predict heart attack.

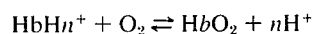
The plugs 18 and 20 operate to close the end of the cylindrical sheath 12 and may be replaced by any technique which similarly provides a closure. The electrodes 22 and 24 are preferably platinized platinum to increase the availability of protons. The excitation source 30 provides a potential to the electrodes 22 and 24. This is preferably in the range of 20 millivolts to 200 millivolts to insure that cathodic oxygen reduction does not take place as will be explained below.

The resistance between the electrodes 22 and 24 is provided by filling the cavity 26 with a mixture 34 that includes a reversible oxygen binding material in an electrolyte solution. Additionally, biasing agents, thixotropants and gascolators may be added as will be explained below. A typical oxygen binding material in the preferred embodiment comprises adult human or bovine haemoglobin (Hb) in a water electrolyte solution. In addition to haemoglobin, cobalt dihistidine has been found to have reversible oxygen binding properties

which make it useful for the oxygen sensitive resistor of the present invention. Other materials for reversible oxygen binding include natural substances like hemerythin, erythrocrucorin, chlorocrucorin, hemocyanin, and myoglobin and synthetic oxygen binding materials.

The concentration of haemoglobin useful in the resistor can vary widely. As one example 10^{-3} moles per liter of Hb in water has been found satisfactory and provides a 10% resistivity change for a 0 to 1 atmosphere oxygen change in the environment.

With reference to FIG. 3 the operation of the oxygen sensitive resistor to reversibly bind rather than to consume oxygen is indicated. A source 40 is provided for generating a low voltage alternating current in the 2-millivolt to 200 millivolt range for application to electrodes 42 and 44 representing the electrodes 22 and 24 in FIG. 1. A barrier 46 is provided between a region 48 intermediate the electrodes 42 and 44 and an environment 50 such as blood or body tissue in which oxygen molecules 52 occur in a predetermined concentration. The barrier 46, which represents the cylindrical sheath 12, is permeable to the oxygen molecules 52, and within a few seconds, the typical diffusion time constant, the normal process of gas diffusion across the barrier 46 will provide a concentration of oxygen molecules 52 within the region 48 which is a function only of the concentration of molecules in the region 50 and not a function of the diffusion rate across the barrier 46. The concentration of oxygen molecules 52 in the region 48 varies the degree to which haemoglobin molecules 54 in the region 48 will bind an oxygen molecule according to the equation indicated in FIG. 4 and below:



Where n is a statistical number reflecting the number of proton released.

The reversible binding reaction results in the release of a free proton 56 as indicated in the equation. While biasing agents to be explained below can be added to the mixture 34 to vary the tendency of the haemoglobin to bind oxygen and release protons, for a given mixture the amount of binding which takes place and correspondingly the number of free protons will be a function of the concentration of oxygen in the region 48 and thus a function of the concentration of oxygen molecules 52 to be measured in the environment 50.

The free protons released from the oxygen binding reaction of FIG. 4 reduce the A.C. impedance between the electrodes 42 and 44 through the reversible exchange of electrons between the free protons as indicated in FIG. 3. A free proton will accept an electron from one of the platinized platinum electrodes 42 or 44 when acting as a cathode and will become attached to the platinized platinum surface as a hydrogen atom. When the electrode acts as an anode, the opposite reaction takes place and an electron is released to the electrical circuit from the hydrogen atom to provide a free proton to the mixture in the region 48.

It is desirable to prevent the reduction of oxygen to form water as indicated in FIG. 5 and in the dashed rectangle 58 of FIG. 3 during the flow of current from the source 40. Therefore the voltage applied to the resistor terminals is kept below a few tenths of a volt to avoid this and other reactions which might lead to a false reading or consume oxygen. While a D.C. source may be employed, an A.C. source is preferred to pre-

vent space charge polarization and a low dielectric constant layer in front of the electrodes. A D.C. source becomes more practical if the haemoglobin is bound to a polymer such as polyacrylamide to prevent drift of the haemoglobin to the anode. Others include cross linked dextran gels, polyamino styrene and acrylic polymers. The binding of proteins such as haemoglobin to polymers of this type is according to well known protein binding reactions. For example, cyanogen bromide is able to bind the amino groups of proteins including haemoglobin to cross linked dextran gels. Dicyclohexyl carbodiimide is able to bind proteins to acrylic polymers through the protein amino groups.

Preferably a first biasing agent is added to the mixture 34 to raise its pH to between approximately 6 to 7.5, the range of 6.5 to 7.0 appearing best as shown in FIG. 8 by path 65 to point 66. This first biasing agent is typically a base such as sodium hydroxide used without buffering. The purpose of this pH change can be explained by reference to FIG. 6 which is a graph representing the Bohr effect with the vertical and horizontal axes representing the ability of haemoglobin to release free protons upon oxygenation as a function of pH. From FIG. 6 it can be seen that the Bohr effect indicates that between pH 6 and 7.5 the capacity of haemoglobin to release protons is at a maximum and accordingly the pH is adjusted in this range. With this pH adjustment made there will be a significant variation in free protons released by the haemoglobin in the mixture 34 as a result of a haemoglobin pK_a change upon oxygenation or oxygen binding.

It is further desirable to add a second biasing agent to the mixture 34 so that the resistor will operate at a more linear portion of its proton concentration versus oxygen pressure curve indicated in FIG. 7. Without a second biasing agent, curve 60 in FIG. 7 approximates the variation in free proton concentration $\bar{y}$, an indication of conductivity, with oxygen pressure which affects oxygen binding. If the expected oxygen pressure is at point 62, however, the curve 60 is inadvantageously positioned to provide the greatest linear variation in $\bar{y}$ with pressure at point 62. The curve 60 is shifted to the position of the curve 64 by the addition of the second biasing agent to bring the linear range of the curve above the point 62.

A typical biasing agent comprises DPG, 2,3 diphosphoglyceric acid, a substance found in the blood for regulating the release of oxygen to the tissues. The effect of adding a second biasing agent is to shift the solution along a line 69 in FIG. 8. Other substances suitable as second biasing agents include inorganic phosphates, ATP, inositol hexaphosphate, and $K_4[Fe(CN)_6]$ as well as $K_3[Co(CN)_6]$. In the case of DPG the free proton concentration $\bar{y}$ is to a first approximation:

$$\bar{y} = Hb(O_2)_4 / (Hb + Hb(O_2)_4 + HbDPG)$$

or the ratio of haemoglobin bound to oxygen to all haemoglobin.

With the addition of DPG, however, the pH is again reduced necessitating the addition of more base. The complete interaction is illustrated by FIG. 8 which is a three axis graph of the affinity of haemoglobin for oxygen as a function of pH and DPG concentration. The Bohr effect indicates that a point 66 on the pH axis is the desired pH point. The addition of DPG moves the mixture to a point 68 below surface 72 near the point of proper slope but at a reduction in pH which is com-

pensated by the addition of more first biasing agent to reach the point 70 at the same pH as point 66.

Additional agents can be added to the mixture 34 such as antioxidants like cholesterol BHT or butylated hydroxytoluene to prevent undesired oxidation reactions. Gascolators such as asbestos may also be placed in the mixture 34 to absorb bubbles formed within the resistors.

While the described application for the present oxygen sensitive resistor is in vivo oxygen detection the same reversible binding reaction may be employed to detect other gases. For example, the described oxygen binding material haemoglobin will also bind carbon monoxide with the release of free protons and accordingly the resistor may be employed to detect toxic carbon monoxide such as in an automobile where oxygen concentrations are relatively stable.

Additionally, while the charge carriers provided by the reversible binding of oxygen have been indicated as protons, it is possible that other charge carriers such as holes or electrons provide the primary conductivity change.

Having described above a preferred embodiment for the present invention it will occur to those skilled in the art that various modifications and alterations can be made to the disclosed structure without departing from the spirit of the invention. It is accordingly intended to limit the scope of the invention only as indicated in the following claims.

What is claimed is:

1. A detector for providing an indication of the relative concentration of oxygen in an environment comprising:

a material selected from the group consisting of haemoglobin, cobalt dihistidine, hemerythin, erythrocyruorin, chlorocruorin, hemocyanin, and myoglobin having the property of reversibly binding oxygen;

the binding of oxygen by said material resulting in the release of charge carriers in said material;

means responsive to the concentration of charge carriers released from said material to provide a representation of the conductivity of said material; and membrane means for exposing said material to said environment to permit reversible binding of oxygen by said material to a degree representative of the concentration of oxygen in said environment.

2. The detector of claim 1 further including:

a solution of the material which binds oxygen and a base in said solution in a concentration which increases the availability of said charge carriers.

3. The detector of claim 2 further including a biasing agent selected from the group consisting of 2, 3 diphosphoglyceric acid, ATP, inositol hexaphosphate, $K_4[Fe(CN)_6]$ and $K_3[Co(CN)_6]$ in a concentration which provides a generally linear variation of material conductivity with sensed oxygen concentration at a predetermined oxygen concentration.

4. The detector of claim 1 wherein said means for providing a representation of said material conductivity includes:

a signal source;

means for applying the signal from said source to said material; and

means for detecting the response to said signal of said material to generate said representation of the conductivity of said material.

5. A carbon monoxide detector comprising:
 a material including haemoglobin having a carbon monoxide affinity which produces a reversible binding of carbon monoxide in response to the exposure of said material to carbon monoxide;
 the reversible binding of carbon monoxide by said material affecting the conductivity of said material;
 membrane means for exposing said material to an environment to permit binding of carbon monoxide from said environment by said material to a degree representative of the concentration of carbon monoxide in said environment;
 means for determining the conductivity of said material in response to the binding of carbon monoxide thereby to provide a representation of the concentration of carbon monoxide in said environment.
6. A gas sensitive resistor for measuring the concentration of oxygen including:
 first and second electrodes;
 a material selected from the group consisting of haemoglobin, cobalt dihistidine, hemerythin, erythrocrucorin, chlorocruorin, hemocyanin, and myoglobin having the properties of reversibly binding oxygen with a resultant change in conductivity;
 a gas permeable membrane enclosing said oxygen binding material for containing said material and permitting the diffusion of oxygen therethrough;
 said first and second electrodes penetrating said membrane to provide electrical contacts to said material whereby the conductivity of said material may be determined.
7. The gas sensitive resistor of claim 6 further including:
 biasing material selected from the group consisting of 2, 3 diphosphoglyceric acid, ATP, inositol hexaphosphate, $K_4[Fe(CN)_6]$ and $K_3[Co(CN)_6]$ in combination with the oxygen binding material to adjust the property of said oxygen binding material to vary the concentration of charge carriers in response to the binding of oxygen to a predetermined condition.
8. The gas sensitive resistor of claim 6 further including a base that raises the pH of said material a predetermined amount.
9. The gas sensitive resistor of claim 6 further including means attached to said electrodes to provide an output indication of the conductivity of said binding material.
10. An oxygen sensitive resistor comprising:

- first and second electrodes;
 a thin membrane of a highly oxygen permeable material;
 a solution containing haemoglobin;
 said membrane enclosing said solution to provide an oxygen penetrable barrier between said solution and its environment;
 means for connecting said electrodes from said solution to said environment;
 means for exciting said electrodes with an electrical potential insufficient for oxygen reduction to form water; and
 means for detecting the flow of current from said exciting means through said electrodes and said solution.
11. The oxygen sensitive resistor of claim 10 including a first further material in combination with said solution to adjust the pH of said solution in the range of between 6 and 7.5.
12. The oxygen sensitive resistor of claim 11 wherein said first further material is a base.
13. The oxygen sensitive resistor of claim 11 further including a biasing agent selected from the group consisting of 2, 3 diphosphoglyceric acid, ATP, inositol hexaphosphate, $K_4[Fe(CN)_6]$ and $K_3[Co(CN)_6]$ in combination with said solution to alter the variation in conductivity of said solution as a function of bound oxygen to provide a generally linear variation in conductivity at a predetermined oxygen concentration.
14. The oxygen sensitive resistor of claim 10 wherein said membrane is a silicone.
15. The oxygen sensitive resistor of claim 10 wherein said first and second electrodes include platinized platinum surfaces in the region contacting said solution.
16. A gas sensitive resistor for measuring the concentration of carbon monoxide including:
 first and second electrodes;
 a material including haemoglobin having the properties of reversibly binding carbon monoxide with a resultant change in conductivity;
 a gas permeable membrane enclosing said carbon monoxide binding material for containing said material and permitting the diffusion of carbon monoxide therethrough;
 said first and second electrodes penetrating said membrane to provide electrical contacts to said material whereby the conductivity of said material may be determined.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,873,267
DATED : March 25, 1975
INVENTOR(S) : Mitchell R. Swartz

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 5, line 15, the third "to" should read --and--.

Signed and Sealed this

tenth Day of February 1976

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks