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GB 2235288 A GB 2022244 A EP 0160768 A1
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(54) **Depth selection optical measurement system, particularly for transcutaneous measurement of substances in body tissues or fluid**

(57) Light from a source (1), such as an LED, is directed towards an object, such as a patients's skin (5), via focussing means (2, 3) and a beam splitter (4). The light passes through the skin and is focussed at a selected depth (d) beneath the surface. Reflected or fluorescent light returning from the subject passes through the focussing means (3) and beamsplitter (4) and then optical selecting means (6), such as a pinhole, so that only light returning from the selected level (d) beneath the surface of the subject is transmitted to the detection means (10), via further lenses (7, 9) and a dispersing element (8). By selecting the level from which measurements are taken, interference from other levels can be reduced. A particular application is a hand-held device for the measurement of bilirubin, where factors which previously could affect the measurement, such as skin pigmentation and thickness, are overcome with this system.

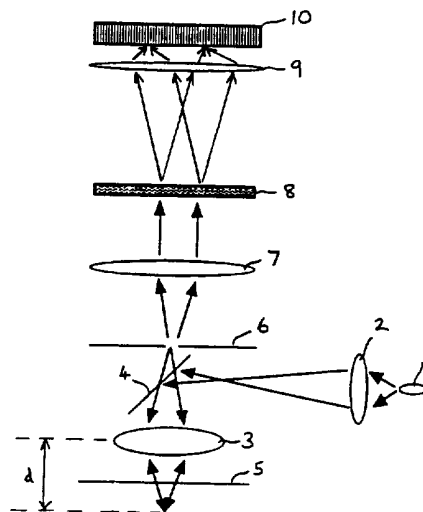


FIG. 1.

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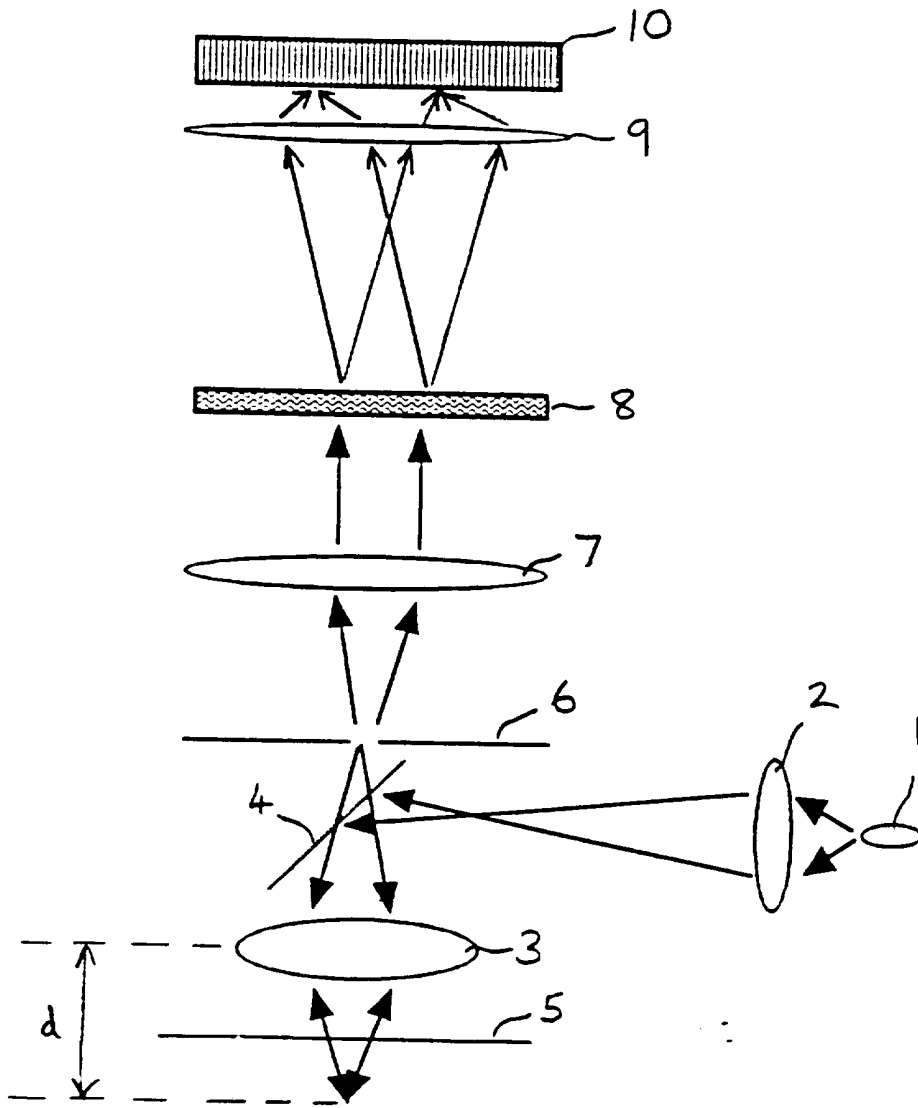


FIG. 1.

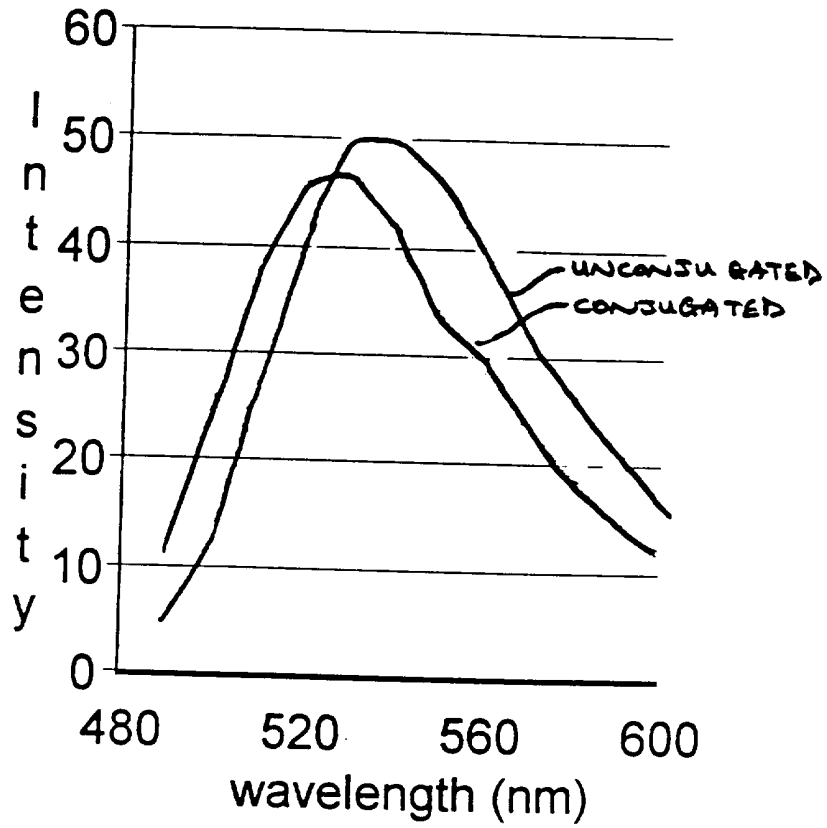


FIG. 2.

TRANSCUTANEOUS MEASUREMENT OF SUBSTANCE
IN BODY TISSUES OR FLUID

This invention relates to apparatus for use in the transcutaneous measurement of a given substance in body tissues or fluids of a subject and to a method of carrying out said measurement.

Measurement of substances within body tissues or fluids, such as blood, are commonly carried out for use in diagnosis or in the monitoring of certain medical conditions. In many cases, such as in the measurement of bilirubin in blood serum, a blood sample is taken for analysis. This is commonly done in the assessment of jaundice in new-born babies by taking a blood sample from the baby's heel. However, this procedure can traumatize the baby, can lead to infection (particularly if repeated samples need to be taken to monitor treatment) and does not provide a reliable measurement at high concentrations of bilirubin.

A number of non-invasive optical techniques have been proposed for measurement of substances such as bilirubin. These involve illuminating the subject skin with one or more wavelengths, detecting the light reflected from the skin, or in some cases transmitted through the body tissues, e.g. through a finger, and analysing the results to measure a spectral characteristic of the reflected or transmitted light caused by the substance to be measured. Such measurements are, however, subject to interference by a number of factors including: skin pigmentation, maturity, the effects of treatment such as phototherapy and the presence of other substances such as blood haemoglobin. In an attempt to overcome these difficulties, complex analyses, usually of several wavelengths, are carried out to try to reduce the effect of the interferences on the desired measurement.

The present invention aims to avoid or significantly reduce such problems.

According to a first aspect of the invention, there is provided apparatus for use in the transcutaneous measuring of a given

substance in body tissues or fluids of a subject comprising: a light source for directing light towards the subject; detection means for detecting light returning from the subject as a result of such illumination; and optical selecting means for transmitting light to the detection means returning only from an area at a selected level beneath or on the surface of the subject.

According to a second aspect of the invention, there is provided a method for transcutaneous measurement of a given substance in body tissues or fluids of a subject in which light is directed towards the subject and light returning from the subject as a result of such illumination is detected by means of optical selecting means which selects only light returning from an area at a selected level beneath or on the surface of the subject.

One particular embodiment of the invention provides apparatus and a method of measuring bilirubin and, in a preferred arrangement, this is carried out by measurement of a fluorescent emission stimulated by the illumination.

Other features of the invention will be apparent from the following description and from the subsidiary claims of the specification.

It should be noted that the term measurement is used to include a measurement sufficient only to identify the presence of a given substance as well as quantitative and semi-quantitative measurements.

The invention will now be further described, merely by way of example, with reference to the accompanying drawings in which:

Figure 1 shows a schematic diagram of apparatus according to one embodiment of the invention; and

Figure 2 is a graph illustrating the optical emission spectrum for an aqueous solution of bilirubin.

The apparatus shown in the Figure comprises an ideal, near point, light source 1, e.g. a light emitting diode or laser diode, the light from which is focussed by means of an optical system comprising first and second lenses 2 and 3 and a beamsplitter 4 in the form of a semi-silvered mirror, towards a subject. As shown, the light passes through the skin 5 of the subject and is focussed at a point a selected distance d from the lens 3 beneath the surface of the skin 5.

Light returning from the illuminated point is collected and focussed by the lens 3 through the beamsplitter 4 and through a spatial filter 6. The illustrated spatial filter 6 is in the form of a pinhole and, as shown, the optical arrangement is such that only light returning from the illuminated point at the distance d from the lens 3 is focussed on and thus able to pass through the pinhole. Light passing through the pinhole is then directed to a detection system comprising a lens 7 which collimates the light, a frequency selecting or dispersing element 8 such as a graduated filter or a transmission grating which acts to separate the component wavelengths of the returning light and a further lens 9 which focusses the separated wavelengths onto detection means 10 in the form of a multi-channel detector such as a photodiode array or charged coupled device.

An output of the detection means 10 representing intensity values for wavelengths detected by the respective detector elements can be analysed, e.g. by maximum entropy or maximum likelihood computations to provide an optimised and least biased measurement of the concentration of the substance being measured.

It will be appreciated that by arranging the optical detection system so that only light returning from an area at a given distance beneath the skin is detected enables a true, transcutaneous measurement to be made. By this means, interference due to skin pigmentation, which is present at or near the surface of the skin, can be avoided by taking measurements from an area beneath the pigment layer.

The ability to select the level of the area from which measurements are taken also helps overcome problems due to treatment by phototherapy

which tends to rapidly reduce bilirubin levels in the fat levels in the skin even though levels in the blood serum may still be high. An initial screening may thus take measurements from the fat level but later measurements may need to be taken from the level of a blood vessel.

Maturity of the skin also affects measurements as the thickness of skin can vary considerably with age, particularly for pre-term babies. The apparatus described thus enables the measurements to be taken from the appropriate level whatever the thickness of the skin.

Also, by taking measurements from a selected area in which the substance being measured is concentrated, interference due to the presence of other substances can be reduced. The spatial filtering thus enables the user to select the level or layer of skin, tissue or body fluid vessel from which measurements are made. Measurement may be taken from areas which may be several millimetres or more beneath the surface of the skin or, in some cases, from the skin surface itself. Depending on the optics used, the area from which measurements are made can be reduced to a size approximately 20 microns in diameter and 20 microns in depth.

The method described thus provides a significant advantage over the prior art which only measures light reflected from the surface of the skin, or on average of reflectance from several different layers of the skin. Similarly, transmission techniques only provide an average measurement for the tissues and fluids through which the light is transmitted.

A pinhole provides a simple but effective spatial filter as described above as only light emanating from the selected area is able to pass through the pinhole; light from other areas is focussed by the lens 3 away from the pinhole and so is unable to pass through the pinhole. By this means, light from other areas is rejected by the optical selection system.

It should be noted that the term pinhole is used to cover actual pinholes and their equivalent, e.g. a small hole made by other means, or a small transparent area within an opaque area.

It will be appreciated that other forms of spatial filter may be used in place of or in addition to a pin hole. One possibility would be to move the lens 3 axially and thus to detect spectral images of several different levels or slices within the subject. Such images can then be processed to construct a 3-dimensional image of the area by means of tomography. A further possibility would be to use a liquid crystal light valve. The provision of a spatial filter also means that only a single light source, rather than a plurality of light sources of different wavelengths, need be used.

The method described in general terms above will now be described in more detail with reference to the measurement of bilirubin.

Bilirubin is a large molecule with certain groups of atoms (chromophores) which absorb blue light and emit a longer wavelength light, by fluorescence, giving a characteristic yellow/orange colour. Babies with jaundice have this yellow/orange colour due to the solubility of bilirubin in skin tissue especially in fat. The red colour of blood is caused by haemoglobin which also absorbs light in the blue part of the spectrum and so interferes with measurements based on the absorption or reflection of light.

The presence of bilirubin can be detected by either measuring its absorbance or its fluorescence. The former can be detected by eye but is notoriously inaccurate and becomes impossible once phototherapy has started. As mentioned above, various skin reflectometers have been proposed to provide a more accurate measurement of skin colour due to bilirubin but these suffer from the problems caused by the various interfering factors discussed above and it is believed that it is these difficulties which have so far prevented an accurate and reliable non-invasive measurement system from being produced.

The method described herein overcomes or reduces these difficulties by the use of spatial filtering, as described above, to select the layer of skin from which measurements are taken. In addition, when measuring bilirubin, its fluorescence emission is detected rather than the reflectance. Furthermore, as will be described in more detail below, analysis of the spectral data obtained is undertaken by statistically optimised data processing software to overcome the remaining interference factors.

The apparatus used for measuring bilirubin uses a blue light emitting diode (LED) which provides a light source closely approximating an ideal point source. Such a diode has a peak output wavelength of 470nm, which corresponds exactly with the absorption maximum of bilirubin molecules and so requires no filters. It can also be powered by a small battery.

For screening for the presence of bilirubin, the optical system comprising lenses 2 and 3 and beamsplitter 4 is arranged to focus light from the LED in a layer of fat approximately 600 microns beneath the surface of the skin, which is the region where the bilirubin concentration is the highest.

Backscattered fluorescent light from the skin is collected by the lens 3 and passes through the beamsplitter 4 to the spatial filter 6 which acts to block light coming from anywhere other than the focus of lens 3. Only light emanating from the region 600 microns beneath the surface of the skin where the lens 3 is focussed is thus transmitted through the spatial filter 6. Melanin pigments which cause skin colour tend to lie closer to the skin surface and so are thus excluded from the measurement.

The light passing through the spatial filter 6 is collimated by lens 7 and then dispersed by a transmission grating 8. An inexpensive plastics grating film having more than 900 grooves per millimetre has been found to provide excellent dispersion of the component wavelengths. The grating 8 thus performs true spectroscopy rather than analysing just one or two wavelengths. The output of the

grating 8 is focussed by a proximity lens 9 onto a photodiode array detector 10 which may, for example, comprise a linear array of 256 elements. The wavelengths emerging from the grating 8 at different angles are each focussed on a respective element of the detector 10 so the outputs from the individual elements of the detector provide a measurement of the intensity of the various wavelengths. Typical spectral emission curves for bilirubin are shown in Figure 2.

Bilirubin normally exists in the body in two main forms, conjugated and unconjugated, and it is the unconjugated bilirubin which is dangerous to young babies as it can cause brain damage if present in high concentrations.

As shown in Figure 2, visible fluorescence can be detected from both forms of bilirubin although the spectral bands are rather broad and overlap substantially.

The outputs of the detector 10 are preferably analysed by microprocessor data reduction techniques to improve specificity, accuracy and reliability. Two particular statistical approaches are favoured: a maximum likelihood method and a factor analysis. Further information on these techniques can be found in a book by D.J. Gardiner and P.R. Graves entitled *Practical Raman Spectroscopy*, Chapter 4, published by Springer-Verlag in 1989 (ISBN 3-540-50254-8) and other references given therein. The maximum likelihood method (also known as the maximum entropy method) performs a Fourier reconstruction of the spectral data subject to the constraints of (i) maximising the entropy content of the solution and (ii) minimising the difference between the sum of component functions of the solution and the spectral dataset. The second approach, that of factor analysis, relies on a least-squares optimisation of known component functions (such as the fluorescence curves for bilirubin and the absorbance curve for melanin). The number of functions fitted and the reliability of the solution obtained is optimised through reference to the auto-correlation matrix for the set of component functions.

By analysing the complete spectral information, it is possible to significantly reduce interferences due to the presence of other substances. With appropriate optimisation of the apparatus and analysis techniques it is believed it may be possible to distinguish between the conjugated and unconjugated forms of bilirubin (as shown in Figure 2).

The apparatus described above thus enables a compact, hand-held, microprocessor controlled unit to be provided for use by doctors, nurses and other medical staff. Such a unit enables rapid, non-invasive measurement of bilirubin levels to be carried out for use in diagnosis, screening and monitoring of jaundice.

A more detailed description has been given in relation to apparatus for measuring bilirubin but it will be appreciated that other substances, such as oxygen, carbon dioxide, glucose, albumen, haemoglobin and cholesterol, may also be measured by similar apparatus.

It will also be appreciated that other light sources can be used in place of the LED or laser diodes referred to above although the light source should preferably approximate to an ideal point source to enable spatial filtering to be carried out as described above.

Other forms of frequency selecting or dispersing elements may also be used, such as a variable filter.

A monolithic multi-channel detector is preferably used rather than a plurality of individual photodiodes. However, a position sensitive detector or other form of detector capable of providing an output indicative of the relevant wavelength(s) sensed may also be used.

Although complete spectral analysis, e.g. of 128 or 256 wavelengths or wavelength bands, is preferably carried out it may, in some circumstances, only be necessary to detect certain specific wavelengths which are found to be characteristic of the substance being measured. In some cases, a measurement of, say, three or four wavelengths may be sufficient to identify a particular substance and, if the substance

emits a very characteristic or particularly strong signal, it may only be necessary to detect a single wavelength. In general, for simple least-squares optimisation, it is necessary to have one more datapoint than the number of components one is trying to distinguish between. Thus, in theory, at least six datapoints would be required to distinguish between the components of a five component system.

CLAIMS

1. Apparatus for use in transcutaneous measurement of a given substance in body tissues or fluids of a subject comprising: a light source for directing light towards the subject; detection means for detecting light returning from the subject as a result of such illumination; and optical selecting means for transmitting light to the detection means returning only from an area at a selected level beneath or on the surface of the subject.
2. Apparatus as claimed in Claim 1 in which the light source approximates to an ideal point source.
3. Apparatus as claimed in Claim 2 in which the light source comprises a light emitting diode or a laser diode.
4. Apparatus as claimed in Claim 1, 2 or 3 in which the detection means is arranged to detect one or more selected wavelengths or wavelength bands.
5. Apparatus as claimed in Claim 4 in which the detection means is arranged to carry out spectral analysis of the light received.
6. Apparatus as claimed in Claim 4 or 5 in which the detection means comprises frequency selecting or frequency dispersing means.
7. Apparatus as claimed in Claim 6 in which the detection means comprises a transmission grating for dispersing light of different frequencies.
8. Apparatus as claimed in any preceding claim in which the detection means comprises a multi-channel detector.
9. Apparatus as claimed in any preceding claim comprising analysis means for analysing an output of the detection means.

10. Apparatus as claimed in Claim 9 in which the analysis means comprises software or firmware which applies one or more predetermined algorithms to the output of the detection means to identify spectral information characteristic of the given substance.
11. Apparatus as claimed in any preceding claim in which the optical selecting means comprises a spatial filter.
12. Apparatus as claimed in Claim 11 in which the spatial filter comprises a pin hole or its equivalent.
13. Apparatus as claimed in any preceding claim having a first optical system for focussing light from the light source in an area at the said selected distance beneath the surface of the subject.
14. Apparatus as claimed in Claim 13 having a second optical system for receiving light returning from the subject and directing this light to the optical selecting means.
15. Apparatus as claimed in Claim 14 in which the first and second optical system comprise a common lens for focussing light at the said selected distance beneath the surface of the subject and for receiving light returning therefrom.
16. Apparatus as claimed in Claim 14 or 15 in which the first and second optical systems comprise a common beamsplitter.
17. Apparatus as claimed in any preceding claim arranged to detect light emitted by fluorescence from the subject resulting from illumination by the said light source.
18. Apparatus as claimed in any preceding claim arranged to provide a measurement of the presence of bilirubin in the subject.
19. Apparatus as claimed in Claim 18 in which the light source emits light having a wavelength of substantially 470nm.

20. Apparatus as claimed in any preceding claim provided in the form of a portable unit.
21. Apparatus for use in transcutaneous measurement of a given substance substantially as hereinbefore described with reference to Figure 1 and/or Figure 2.
22. A method for transcutaneous measurement of a given substance in body tissues or fluids of a subject in which light is directed towards the subject and light returning from the subject as a result of such illumination is detected by means of optical selecting means which selects only light returning from an area at a selected level beneath or on the surface of the subject.
23. A method for transcutaneous measurement of a given substance in body tissues or fluids using apparatus as claimed in any of Claims 1 to 21.
24. A method for transcutaneous measurement of a given substance in body tissues or fluids substantially as hereinbefore described.

Amendments to the claims have been filed as follows

1. Apparatus for use in transcutaneous measurement of a given substance in body tissues or fluids of a subject comprising: a light source for directing light towards the subject; light detection means; and an optical system comprising focussing means for focussing light returning from the subject and optical selecting means through which light from said focussing means is passed, arranged such that only light returning from an area at a selected level beneath or on the surface of the subject is transmitted to the detection means.
2. Apparatus as claimed in Claim 1 in which the light source approximates to an ideal point source.
3. Apparatus as claimed in Claim 2 in which the light source comprises a light emitting diode or a laser diode.
4. Apparatus as claimed in Claim 1, 2 or 3 in which the detection means is arranged to detect one or more selected wavelengths or wavelength bands.
5. Apparatus as claimed in Claim 4 in which the detection means is arranged to carry out spectral analysis of the light received.
6. Apparatus as claimed in Claim 4 or 5 in which the detection means comprises frequency selecting or frequency dispersing means.
7. Apparatus as claimed in Claim 6 in which the detection means comprises a transmission grating for dispersing light of different frequencies.
8. Apparatus as claimed in any preceding claim in which the detection means comprises a multi-channel detector.
9. Apparatus as claimed in any preceding claim comprising analysis means for analysing an output of the detection means.

10. Apparatus as claimed in Claim 9 in which the analysis means comprises software or firmware which applies one or more predetermined algorithms to the output of the detection means to identify a spectral information characteristic of the given substance.
11. Apparatus as claimed in any preceding claim in which the optical selecting means comprises a spatial filter.
12. Apparatus as claimed in Claim 11 in which the spatial filter comprises a pin hole or its equivalent.
13. Apparatus as claimed in any preceding claim in which the optical system comprises means for focussing light from the light source on the said area at the selected distance beneath the surface of the subject.
14. Apparatus as claimed in Claim 13 in which the optical system comprise a lens which acts to focus light at the said selected distance beneath the surface of the subject and receive light returning therefrom.
15. Apparatus as claimed in any preceding claim in which the selected level is determined by adjustment of the optical system.
16. Apparatus as claimed in any preceding claim in which said adjustment is effected by axial movement of a lens and/or of the optical selecting means.
17. Apparatus as claimed in any preceding claim arranged to detect light emitted by fluorescence from the subject resulting from illumination by the said light source.
18. Apparatus as claimed in any preceding claim arranged to provide a measurement of the presence of bilirubin in the subject.

19. Apparatus as claimed in Claim 18 in which the light source emits light having a wavelength of substantially 470nm.
20. Apparatus as claimed in any preceding claim provided in the form of a compact, hand-held unit.
21. Apparatus for use in transcutaneous measurement of a given substance substantially as hereinbefore described with reference to Figure 1 and/or Figure 2.
22. A method for transcutaneous measurement of a given substance in body tissues or fluids of a subject in which light is directed towards the subject and light returning from the subject as a result of such illumination is focussed and passed through optical selecting means such that only light returning from an area at a selected level beneath or on the surface of the subject is detected.
23. A method for transcutaneous measurement of a given substance in body tissues or fluids using apparatus as claimed in any of Claims 1 to 21.
24. A method for transcutaneous measurement of a given substance in body tissues or fluids substantially as hereinbefore described.



Application No: GB 9523524.8
Claims searched: 1 and 22

Examiner: James Porter
Date of search: 3 October 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:
UK CI (Ed.O): G1A (AAMA, AAMX, ACDL, ACDX, ACJT, ACJW, ACJX, ADMX)
Int CI (Ed.6): A61B 5/00;
G01N 21/25, 21/27, 21/31, 21/35, 21/49, 21/53, 21/62, 21/64
Other: Online database: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	GB2235288 A (NRDC) Embodiment of figure 4.	1, 3-10, 22, 23
Y	" "	18-20
Y	GB2022244 A (MINOLTA) Whole document.	18-20
X	EP0160768 A1 (BATELLE) p13, line 10 onwards. Also figure 2.	1, 3, 4, 5, 9-12, 22, 23
Y	" "	18-20
Y	US4029085 (DEWITT) Whole document.	18, 19

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.