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Dick

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(54) **NON-INVASIVE MEASUREMENT OF SKIN BILIRUBIN LEVEL**

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(73) Assignee: **Medick S.A.**, Pierrelaye (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 435 days.

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(52) **U.S. Cl.** **356/39**; 600/306; 600/315
(58) **Field of Search** 356/39, 394; 600/315, 600/306, 310, 317, 320–323

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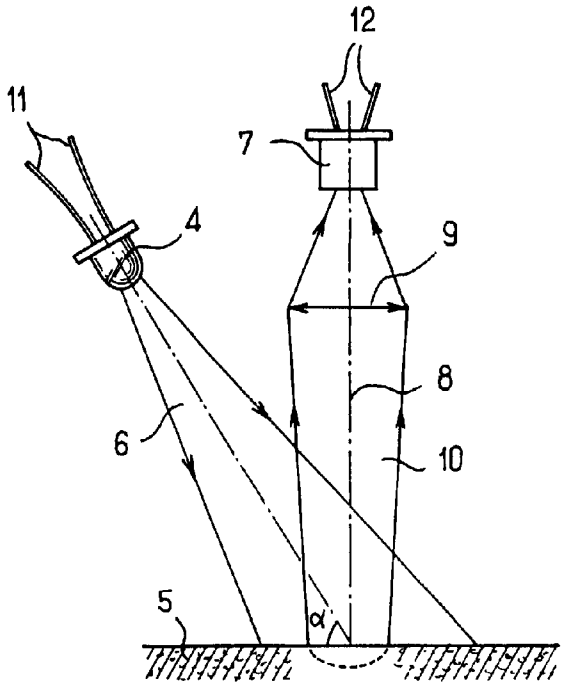
(57) **ABSTRACT**

The invention concerns a method and a device for non-invasive measurement of a tissue and in particular of the skin bilirubin level. The inventive device is characterized in that it comprises: a reading head (**1**) capable of sending several flashes of various specific wavelengths towards the tissue (**2**) to be examined and of receiving and measuring in return the reflected light; a calculator, such as a microprocessor, capable of calculating for each wavelength the amount of reflected light and bring it to a value calculated proportionally to a reference value identical for a predetermined wavelength; and a comparator for comparing the calculated value to a table of reference values.

12 Claims, 3 Drawing Sheets



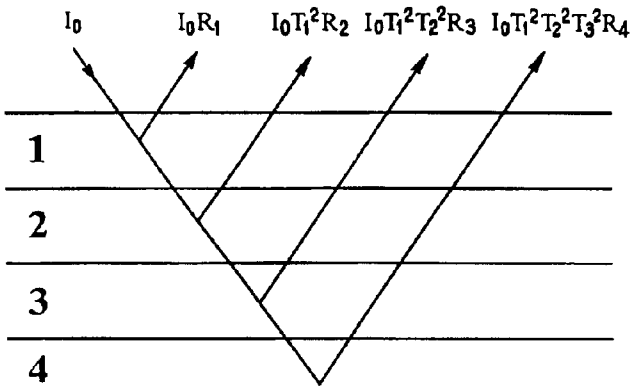


FIG_1

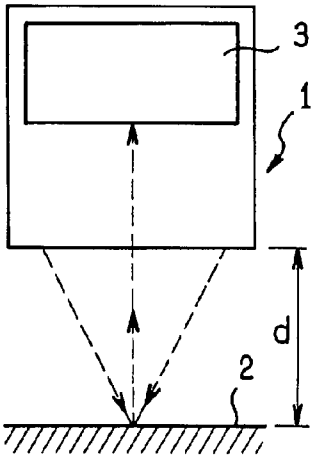


FIG_3

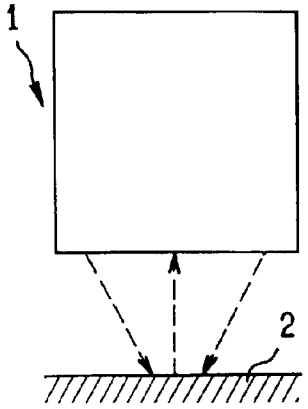


FIG_4

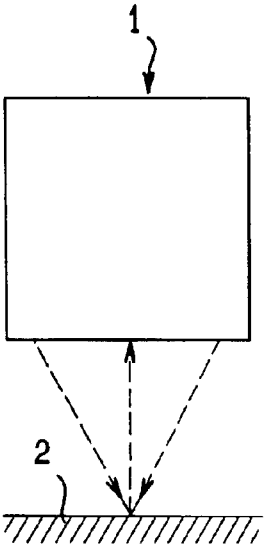


FIG_5

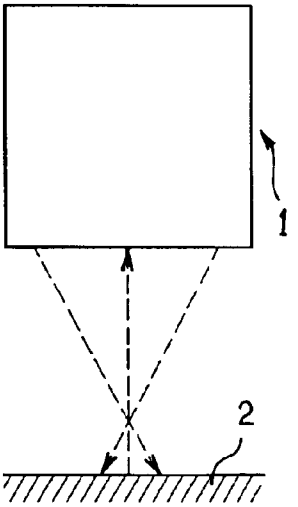


FIG_6

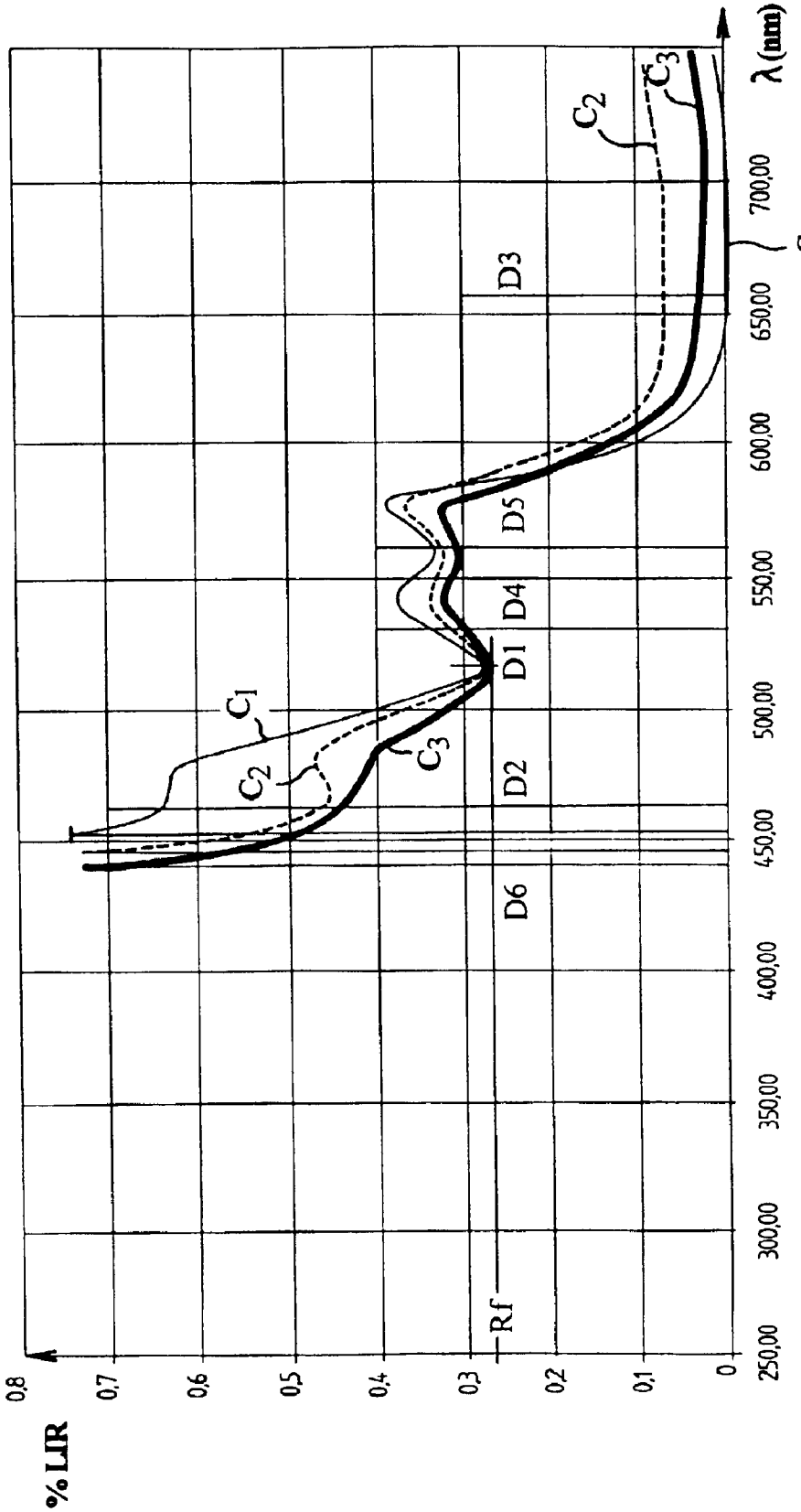

% LIR
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
250,00
300,00
350,00
400,00
450,00
500,00
550,00
600,00
650,00
700,00
λ (nm)
Rf
D1
D2
D3
D4
D5
D6
C1
C2
C3

FIG_2

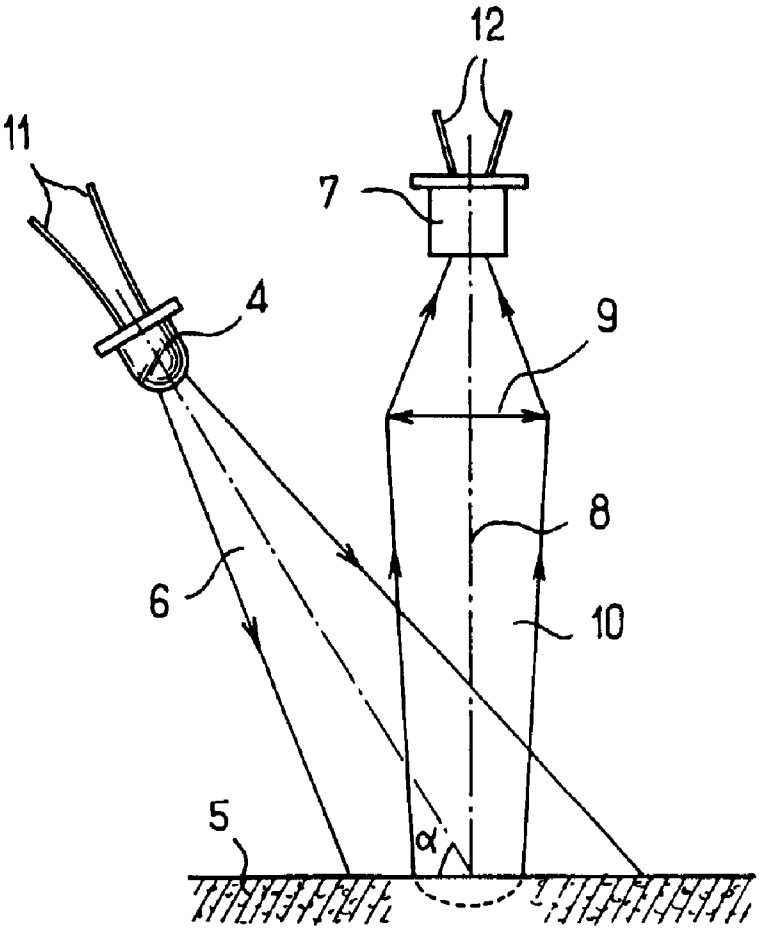


FIG_7

NON-INVASIVE MEASUREMENT OF SKIN BILIRUBIN LEVEL

This invention relates to a process and to a device for the non-invasive analysis of a tissue, such as the skin for instance.

Many works have shown that it was possible, by sending white light on a tissue such as the skin or a plant tissue and analyzing the reflected light, to obtain some information concerning the nature of the tissue and particularly the concentration of its various constituents. The general principle is that the constituents of the various wavelengths that form the white light are reflected differently depending on the constituents encountered by the light. A fine and continuous analysis of the reflected light should thus enable to obtain a fairly precise non-invasive analysis of the tissue being examined.

The devices already known that operate according to this principle require nonetheless a costly optical analysis equipment such as spectrographs and powerful calculators to analyze the collected data, as well as a delicate calibration of the various instruments.

This invention offers a process and a measuring device that overcome these difficulties of implementation.

To this effect, the process of this invention for the measurement of a skin constituent level, particularly that of the bilirubin level in the skin, is characterized in that are performed a first measurement of the reflection of the light with a first given wavelength representative of the measurement to be performed, and at least the measurement of a second reflection of the light of a predetermined wavelength used as reference for which is determined a reflection reference unit value by calculating the ratio k between the reflection measured on the tissue for this second wavelength and the reflection measured on a standard for this same second wavelength; and in that the level of the constituent to be evaluated is deduced by measuring the reflection of the first given wavelength according to a table of predetermined known values for this first wavelength, after correction by the factor k previously measured said reflection measurement so as to obtain the value to be compared with the table of reference values.

A device according to this invention is itself characterized in that it consists of:

a reading head that can send successively several flashes with various defined wavelengths toward the tissue to be examined, and receive and measure in return the reflected light,

a calculator such as a microprocessor, that can calculate for each wavelength the quantity of reflected light and bring it to a value calculated proportionally to a reference value identical for a given predetermined reference wavelength,

a comparator enabling to compare the value so calculated to a table of reference values.

Advantageously, this device uses electro-luminescent diodes for sending sequential flashes of determined wavelengths.

The invention and its implementation will become more apparent from the following description, together with the accompanying drawings.

In the drawings:

FIG. **1** shows the principle underlying the optical reflection of the light by the skin.

FIG. **2** shows three LIR curves recorded for three subjects, said curves having been subjected to a mathematical treatment so as to level them for a given wavelength threshold.

FIG. **3** is a diagram of the principle of a device according to this invention.

FIGS. **4**, **5** and **6** show the principle underlying the practical use of said device.

FIG. **7** is a diagram of a variation in the implementation of a measuring device according to this invention.

FIG. **1** is a reminder of the principle concerning the propagation of light and of its reflection by the skin. This principle is explicited , in particular, in the publication of Dawson, Barker and al.: "a theoretical and experimental study of the in vivo absorption and diffusion of light by the skin" (Phys. Med. Biol. 1980, vol. 25, n°4, pages 695–709).

Considering successively that the layer **1** is the stratum corneum, that the layer **2** corresponds to the epidermis, that the layer **3** corresponds to the derm and the layer **4** to the hypodermis, if we reference respectively as R1, R2, R3 and R4 the reflection factors of the successive layers and as T1, T2, T3 and T4 the transmission factors of these same layers, the reflected light is globally such as:

$$I=I_o R_1+I_o T_1^2 R_2+I_o T_1^2 T_2^2 R_3+I_o T_1^2 T_2^2 T_3^2 R_4 \ldots$$

If the skin is not too dry, the reflection factors R1, R2 and R3 are notably inferior to R4, while the global reflection is reduced to:

$$R=(I/I_o)\#T_1^2 T_2^2 T_3^2 R_4 \ldots$$

Taking the Neperian logarithm (LN) of the inverse of the reflection, LIR, leads to:

$$LIR=-LN(T_1^2)-LN(T_2^2)-LN(T_3^2)-LN(R_4) \ldots$$

This LIR, represented for all the wavelengths, enables to display all the skin characteristics. It becomes thus possible to draw curves and to deduce from them the skin qualities by analyzing the correspondent absorption bands that characterize the various constituents of the skin, and to deduce for instance the bilirubin, hemoglobin, melanin, etc., levels.

As already mentioned, the practical application of this theory comes up against considerable equipment and calibration difficulties, since the curves vary greatly from one subject to another, depending in particular on the subject's own pigmentation.

With this invention, it becomes nonetheless possible to overcome these difficulties, related to the very different skin reactions from one subject to another, by "tuning" all the curves to the level of a reference threshold for a specific predetermined wavelength λ_f used as a reference, which enables to perform a qualitative and quantitative analysis without having to draw the curves (thus avoiding the need for a spectrograph), just by recording a few measurement points for precise and relevant wavelengths, after a simple calculation of threshold setting.

Referring now to FIG. **2**, in which were shown three curves with, in ordinate the absorption measured in LIR % as a function of the wavelength of the light received by the skin of three different subjects. Yet, these curves were treated mathematically, in order to standardize them and to show the operation of the device and the process of this invention.

To obtain the curves in FIG. **2**, four successive steps are taken.

First step. A calibration is carried out by measuring the reflection on a "gray" or "white" "standard" (e.g. a compacted powder of barium sulfate). For good results, and in particular to eliminate possible drifts in the diodes, as time goes on and/or in response to the room temperature, said calibration/standardization is performed before each measurement on the "gray" or "white" chosen standard.

In the illustrated example, it was assumed that six successive measurements were performed respectively for the wavelengths: 520 nm, 460 nm, 660 nm, 545 nm, 575 nm, and 430 nm. These specific wavelengths can actually be emitted by electro-luminescent diodes DEL of suitable quality.

FIG. **3** shows a diagram of the measuring device. Here the device **1** comprises electro-luminescent diodes DEL that send a light beam, for example slightly conical and convergent (as shown by the arrows), on the skin **2** of the subject to be examined. The reflected light, essentially perpendicular to the subject's skin, is received by a detector **3** that analyzes the intensity of the radiance received. The use of a conical beam is advantageous on several accounts: it allows for the elimination of most of the specular reflection and also for a precise determination of an optimum distance d between the position of the device **1** and the skin, by measuring the reflection when the light output is essentially reduced to a point on the skin **2**. The cone angle is advantageously comprised between 30° and 50°, e.g. around 45°.

The detector of the measuring device records an intensity of the reflection factor:

$|_{OD1}$ for the diode D**1**,

$|_{OD2}$ for the diode D**2**, . . .

$|_{OD6}$ for the diode D**6**.

Second step. An operation is performed to measure the reflection on the skin to be tested.

During the measuring process on the skin of a child "x," the detector of the measuring device records an intensity of the reflection factor:

$|_{xD1}$ for the diode D**1**,

$|_{xD2}$ for the diode D**2**, . . .

$|_{xD6}$ for the diode D**6**.

Third step. Now takes place the mathematical "standardization" treatment so that, for a given reference wavelength, in this case that of the first diode D**1** at 520 nm, all the curves go through the same absorption level point, or reflection factor, measured in ordinate.

The calculator, advantageoulsy a microprocessor, performs the following standardization calculations:

$(|_{xD1}/|_{OD1})=R_{x1}$ for the diode D**1**

$(|_{xD2}/|_{OD2})=R_{x2}$ for the diode D**2**

. . .

$(|_{xD6}/|_{OD6})=R_{x6}$ for the diode D**6**

Then the operation is such that, for the reference wavelength selected as relevant λ_{ff}, all the reflection factors R_{x1f} are equal to a reference value Rf.

$R_{x1f}=R_{0f}$ 4 $k=R_{0f}/R_{x1f}$

The various reflection factors R_{xn} are then multiplied by the corresponding factor k to obtain the standardized factors R_{xnf}.

$R_{x2f}=k\ R_{x2}$

$R_{x6f}=k\ R_{x6}$

By bringing, for this reference wavelength, all the reflection levels to the same threshold level Rf, it becomes possible to operate a direct reading of the level under examination, for instance the bilirubin level, by simple reading of the corresponding standardized LIR.

Fourth step. From the standardized reflection factors, the microprocessor computes the LIRs:

$LIR_{x1}=\text{Log}\ (1/R_{x1f})=\text{Log}\ (1/R_f)=\text{Constant}$

$LIR_{x2}=\text{Log}\ (1/R_{x2f})$

. . .

$LIR_{x6}=\text{Log}\ (1/R_{x6f})$

The LIRs so established enable a comparison with the spectral curves, i.e in the illustrated example three curves corresponding to the various reflection factors of three subjects under examination. In the example of the illustrated curves, the whole curves were actually obtained from a spectrograph analyzing continuously the wavelengths within a range from 430 nm to 750 nm, in order to have a more accurate representation of the path of these curves, though they are not actually necessary for the analysis measurements of the various constituents of the skin, as will be explained in detail thereafter, in reference to the three given examples of measurement.

Back to FIG. **2**, for a wavelength of 460 nm, can be found on the three curves respectively C**1**, C**2**, C**3**, corresponding absorption rates of about 0.75, 0.55 and 0.5 measured in % standardized LIR. The simple measurement of said absorption level enables, as can be noted, to deduce that for the subject of the curve C**2**, the bilirubin level is normal while for the subject of the curve C**1**, the bilirubin level is high and for the subject of the curve C**3**, the bilirubin level is too low. These data (these percentages of LIR) can be simply recorded in a table of reference values already tested and known.

Likewise, it is possible to evaluate the hemoglobin content from the reflection rate of the light emitted by the diodes D**4** at 545 nm or 550 nm and D**5** at 575 nm. Measurements of the reflection level in the emission area of the diode D**6** at around 430 nm would add further precision to the results.

The skin pigmentation can be evaluated through the level of the reflection rates vis-à-vis the light emitted by the diode D**3** at around 660 nm (within a range from 620 to 780 nm). Actually, it is observed that beyond this, the LIR curve is essentially a straight line, so that the determination on this curve of two points distant enough from this wavelength, e.g. about 620 nm and 780 nm, will enable to determine precisely the corresponding pigmentation characteristic: African, European, Asian, etc. type.

With the process of this invention, it is not necessary to trace the whole curves as it is possible to just resort to limited measurements for wavelengths that are precise and well-defined. This is because the temporary fluctuations and colors or pigmentations specific of the various skins are overcome by the "standardization" process already described.

Moreover, since no mechanical pressure is applied to the tissue to be examined, the measurement is not distorted, as would be the case if the measuring of a skin hemoglobin level were done through a pressure applied to the skin that would drive the blood away from the measurement area.

Thus, when one wants to measure the bilirubin level of the light skin of a quiet baby, this bilirubin level is evaluated directly from the LIR_{x2} measured with the diode D**2**, by carrying out the operation $LIR_{x2}-LIR_{x1}$.

If the bilirubin level is measured on a colored skin [non-European ethnic group] and/or a restless baby [blood rush in the skin area], the indications for the LIR_{x2} are automatically corrected in the same way because of the subtraction $LIR_{x2}-LIR_{X1}$, and because the value LIR_{x1} was standardized by the operation previously described (same standardized reflection threshold Rf for the diode D**1**, standardized for each measurement).

In reference to FIG. **4** to **6** is shown how, because of the use of a conical light beam, it was immediately possible, as shown in FIG. **5**, to determine the right measurement distance d between the device and the subject's skin. When the device is too close, as shown in FIG. **4**, the skin does not display the pinpoint as in FIG. **5**, and neither does it if the device is too far, as shown in FIG. **6**.

The device can thus be designed so that, when it is directed toward the skin, the lighting is only triggered when the device is at the right distance, i.e. when the light beam converges essentially into a pinpoint on the skin.

According to the variation of this embodiment shown in FIG. **7**, the electro-luminescent diodes DEL with the reading head shown in the diagram **4**, light the skin surface shown in **5**, from an angle alpha (α), advantageouly comprised between 30° and 60°, for instance 45°; the light beam **6** is reflected on the skin; by setting the sensor **7** of the device reading head in the axis **8** perpendicular to the surface **5** of the lit area of the skin, only the part of the light coming from the electro-luminescent diode **4** that is diffused by the skin is detected by the sensor **7**, and not the light reflected on the skin surface, which depends on the brightness of the skin. It is thus possible to obtain more reliable data concerning the characteristic to be measured: bilirubin level, hemoglobin level, etc.

In FIG. **7**, a lens **9** was brought in the path of the beam **10** of the light diffused by the skin in order to increase the light power detected by the sensor **7**. **11** and **12** represent respectively the power wires of the electro-luminescent diodes **4** and of the light output coming from the sensor **7**.

Advantageously, if five or six electro-luminescent diodes DEL are used that emit suitable wavelengths such as previously defined, the diodes will preferably be powered successively so that the sensor may successively perform the measurements of the reflection levels needed for the analysis of the results. Prior to each measurement performed on a tissue to be analyzed, the device will have been calibrated, as previously mentioned, upon a "gray" or "standard white", which will allow to calculate the coefficient k such as previously mentioned.

Although the invention was described more precisely for the analysis of the bilirubin level contained in the skin, or other skin constituents such as pigmentation, hemoglobin, etc., the principle of this invention can be extended to the analysis of any tissue, provided that will be determined the precise wavelength(s) for which the reflection level must be recorded to obtain a relevant measurement, and the wavelength on which to tune all the curves so as to obtain the standardization of said curves.

What is claimed is:

1. Process for the measurement of the level of a tissue constituent, characterized in that is/are measured a first light reflection with a first given wavelength that is representative of the measurement to be performed and at least a second measurement of the light reflection for another second predetermined wavelength that will serve as a reference unit value Rf, by calculating the coefficient k between the reflection measured on the tissue for this second wavelength and the reflection measured on a standard for this same second wavelength, and in that the level of the constituent to be evaluated is deduced from the measurement of the reflection of the first wavelength according to a table of predetermined values known for this same first wavelength, after correction by the factor k previously measured of said reflection measurement, so as to obtain the value to be compared to the table reference values, said unit value and said second wavelength determining a point through which will go all the LIR curves after standardization.

2. Process according to claim **1**, characterized in that, for an individual's skin, the second wavelength selected is λ=520 nm.

3. Process according to claim **2**, characterized in that, for the measurement of the skin bilirubin level, the wavelength selected is λ=460 nm.

4. Device for the measurement of the level of a tissue constituent, characterized in that it comprises:

a reading head capable of sending successively several flashes of various predefined wavelengths toward the tissue to be examined as a conical beam having a cone angle between 30° and 50° and of receiving and measuring in return the reflected light,

a calculator, capable of calculating for each wavelength the amount of reflected light and of bringing it to a value calculated proportionally to a reference value identical for a predetermined wavelength,

a comparator for comparing the calculated value to a table of reference values.

5. Device according to claim **4**, characterized in that it comprises electro-luminescent diodes as elements to send successive flashes of various specific wavelengths.

6. Device according to claim **4**, characterized in that the light wavelength used to measure the reference value is about 520 nm.

7. Device according to claim **6**, characterized in that the light wavelength used to measure the bilirubin level is about 460 nm.

8. Device according to claim **6**, characterized in that the light wavelength used to measure the skin pigmentation is comprised between 620 and 780 nm.

9. Device according to claim **6**, characterized in that the light wavelength used to measure the skin hemoglobin are two wavelengths or about 545 and 575 nm.

10. Device according to claim **6**, characterized in that the light wavelength used to measure the skin hemoglobin is a wavelength of about 550 nm.

11. Device according to claim **6**, characterized in that the light wavelength used to measure the skin hemoglobin is a wavelength of about 430 nm.

12. Device according to claim **6**, characterized in that the light wavelengths used to measure the skin hemoglobin are two wavelengths of about 550 nm and 430 nm.

* * * * *

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(12) **United States Patent**
Samuels et al.

(10) **Patent No.: US 6,882,873 B2**
(45) **Date of Patent: Apr. 19, 2005**

(54) **METHOD AND SYSTEM FOR DETERMINING BILIRUBIN CONCENTRATION**

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(73) Assignee: **Respironics, Inc.**, Murrysville, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/303,832**

(22) Filed: **Nov. 26, 2002**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/589,403, filed on Jun. 8, 2000, now abandoned, which is a continuation-in-part of application No. 09/286,649, filed on Apr. 6, 1999, now Pat. No. 6,192,734, which is a continuation of application No. 09/054,490, filed on Apr. 3, 1998, now Pat. No. 5,924,981, which is a continuation-in-part of application No. 08/904,766, filed on Aug. 1, 1997, now Pat. No. 6,045,502, which is a continuation-in-part of application No. 08/621,182, filed on Mar. 21, 1996, now abandoned, which is a continuation-in-part of application No. 08/587,949, filed on Jan. 17, 1996, now Pat. No. 5,860,421.

(51) **Int. Cl.**[7] **A61B 5/00**
(52) **U.S. Cl.** **600/315**; 600/322
(58) **Field of Search** 600/309–310, 600/322, 315

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Primary Examiner—Eric F. Winakur
Assistant Examiner—Matthew J Kremer
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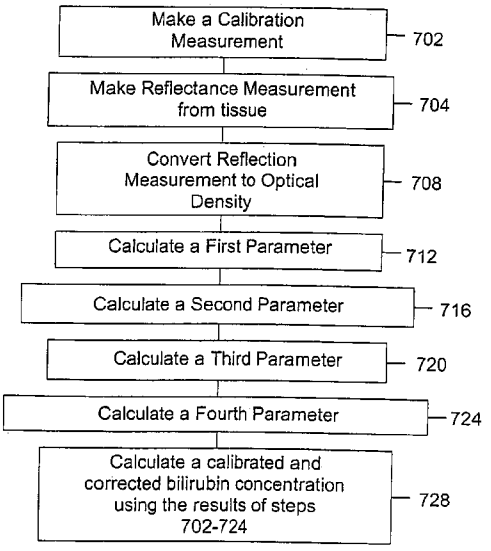
(57) **ABSTRACT**

A system and method embodying the invention can be used to detect a characteristic or condition of a patient. A method embodying the invention may include the steps of illuminating a portion of a skin of the patient with light, detecting a frequency spectrum of light scattered from the skin, determining, from first and second portions of the spectrum, a first parameter indicative of a blood content of the skin and a second parameter indicative of a melanin content of the skin, determining, from a third portion of the spectrum, a third parameter indicative of an uncorrected bilirubin concentration, and calculating a corrected bilirubin concentration based on the first, second and third parameters.

45 Claims, 31 Drawing Sheets



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5,353,790	A		10/1994	Jacques et al.
5,355,880	A		10/1994	Thomas et al.
5,360,004	A		11/1994	Purdy et al.
5,365,925	A		11/1994	Lee
5,370,114	A		12/1994	Wong et al.
5,371,358	A		12/1994	Chang et al.
5,372,135	A		12/1994	Mendelson et al.
5,383,452	A		1/1995	Buchert
5,411,032	A		5/1995	Esseff et al.
5,416,816	A		5/1995	Wenstrup et al.
5,435,309	A		7/1995	Thomas et al.
5,458,140	A		10/1995	Eppstein et al.
5,487,607	A		1/1996	Makita et al.
5,590,052	A		12/1996	Kopf-Sill et al.
5,792,049	A		8/1998	Eppstein et al.
5,830,132	A		11/1998	Robinson
5,845,282	A	*	12/1998	Alley et al. 707/10
5,902,246	A		5/1999	McHenry et al.
5,924,981	A		7/1999	Rothfritz et al.
6,045,502	A	*	4/2000	Eppstein et al. 600/315

* cited by examiner

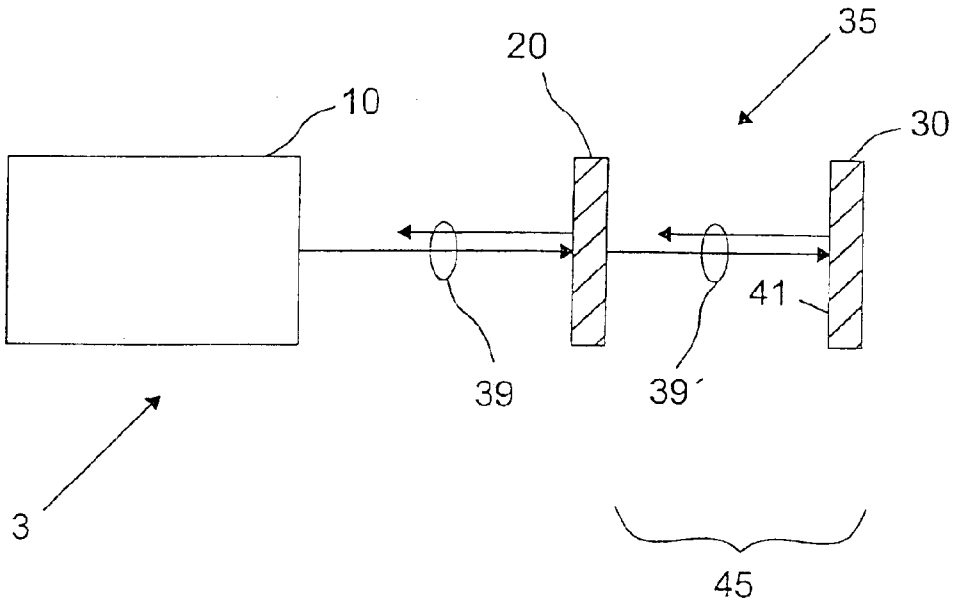

FIG. 1A

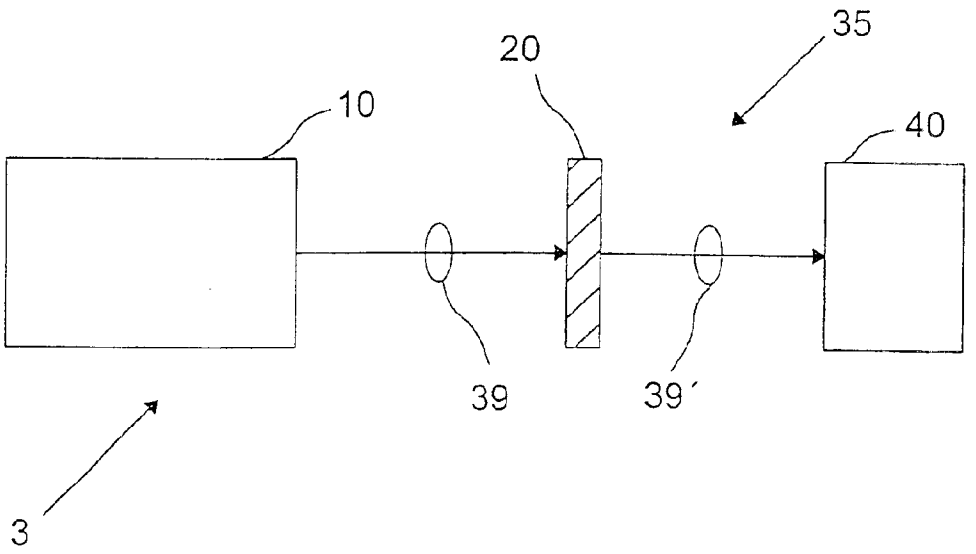

FIG. 1B

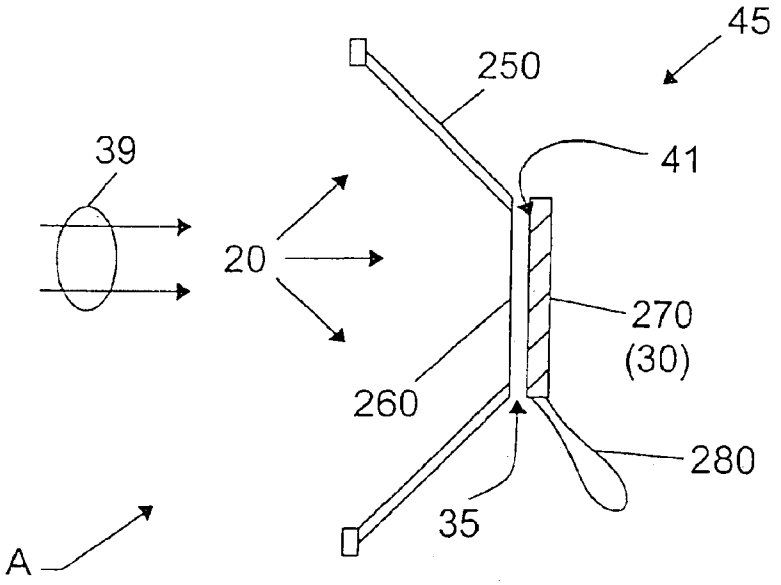
45
250
41
39
20
270
(30)
260
280
35
A

FIG. 2A

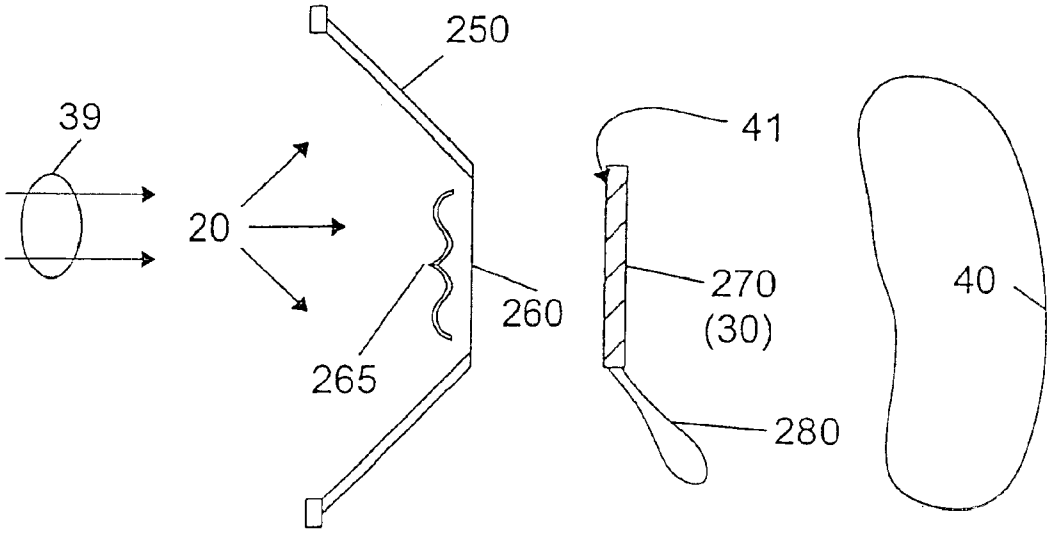
250
39
41
20
270
(30)
40
260
265
280

FIG. 2B

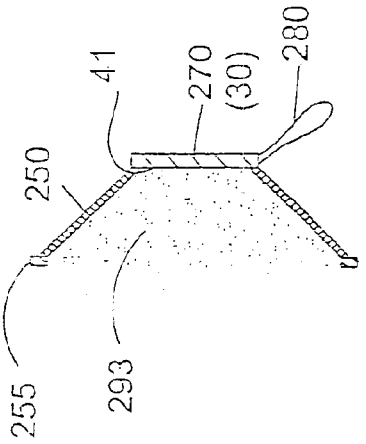

FIG. 2D

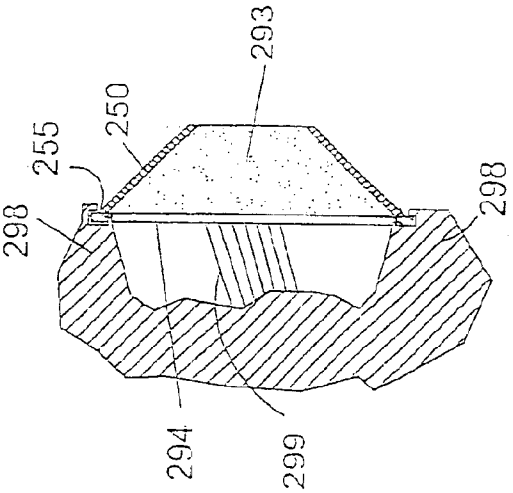

FIG. 2E

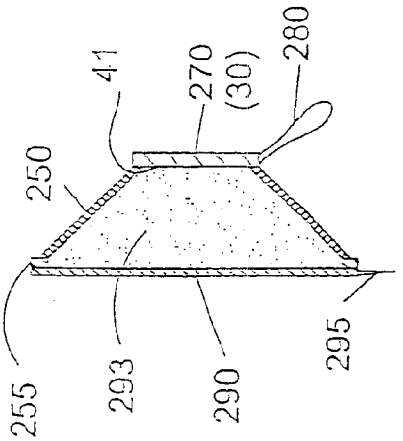

FIG. 2C

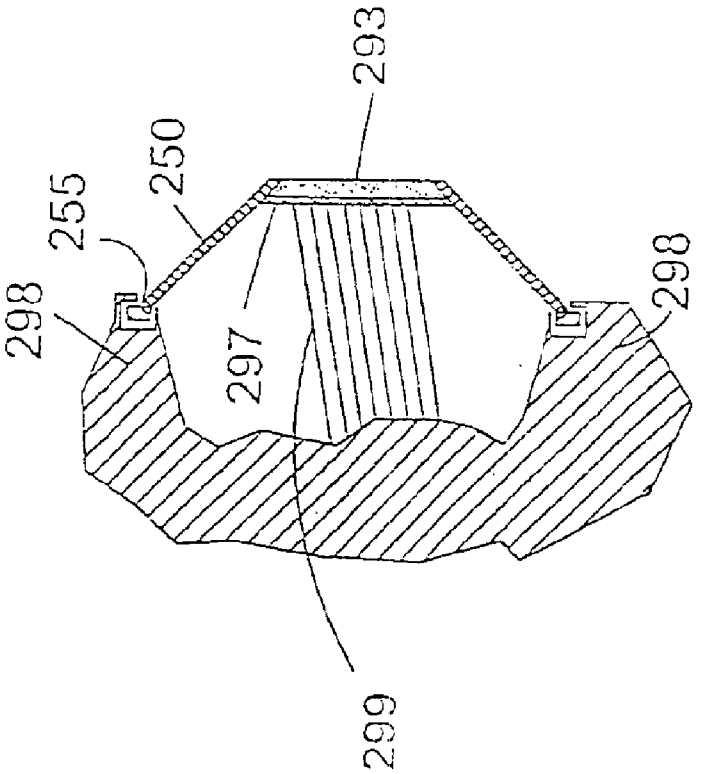

FIG. 2G

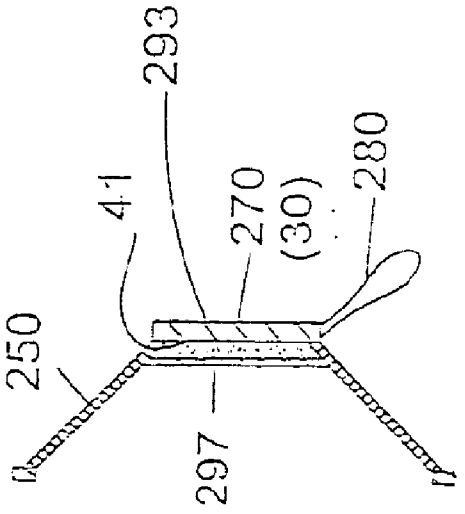

FIG. 2F

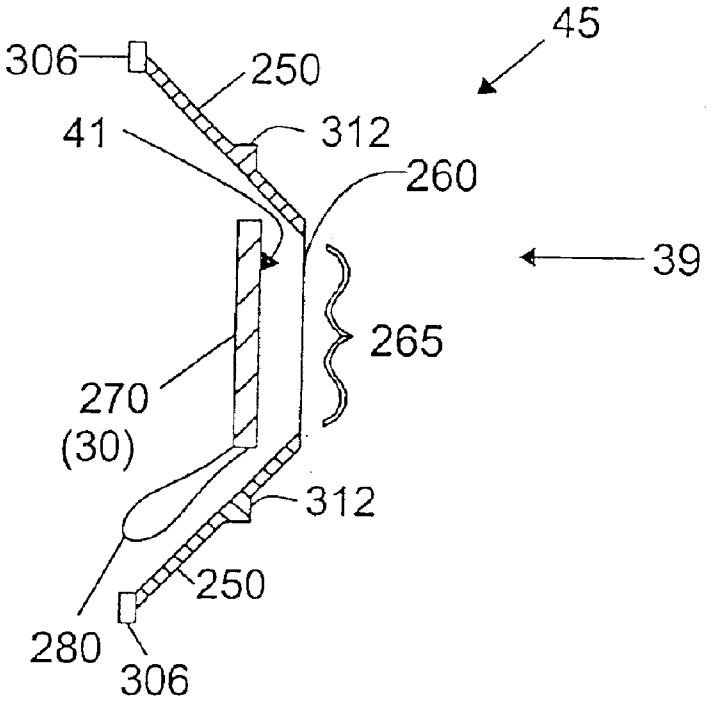
45
306
250
41
312
260
39
265
270
(30)
312
250
280
306

FIG. 3A

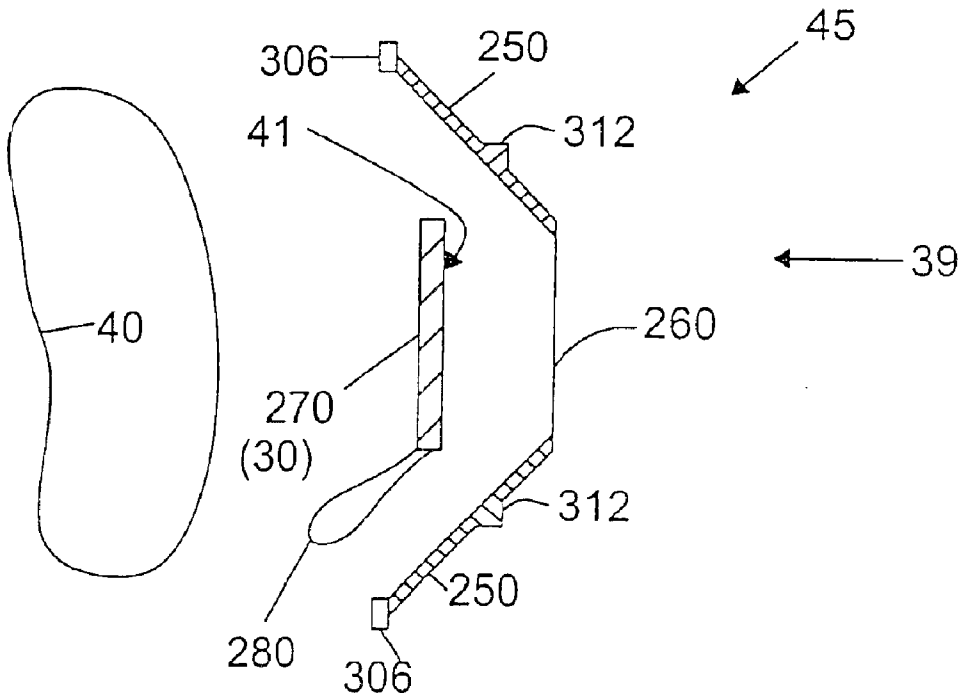
45
306
250
41
312
39
40
260
270
(30)
312
250
280
306

FIG. 3B

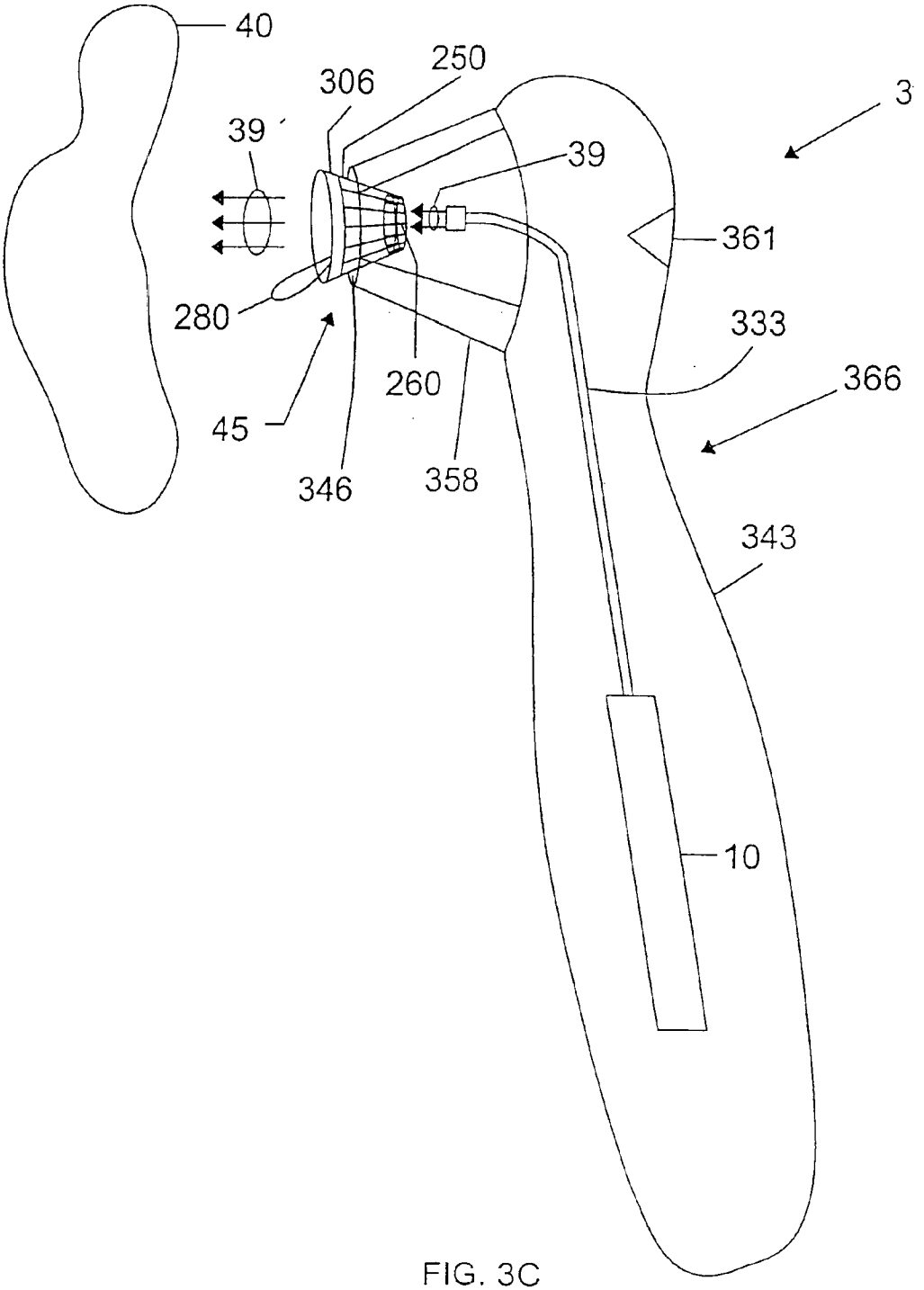

FIG. 3C

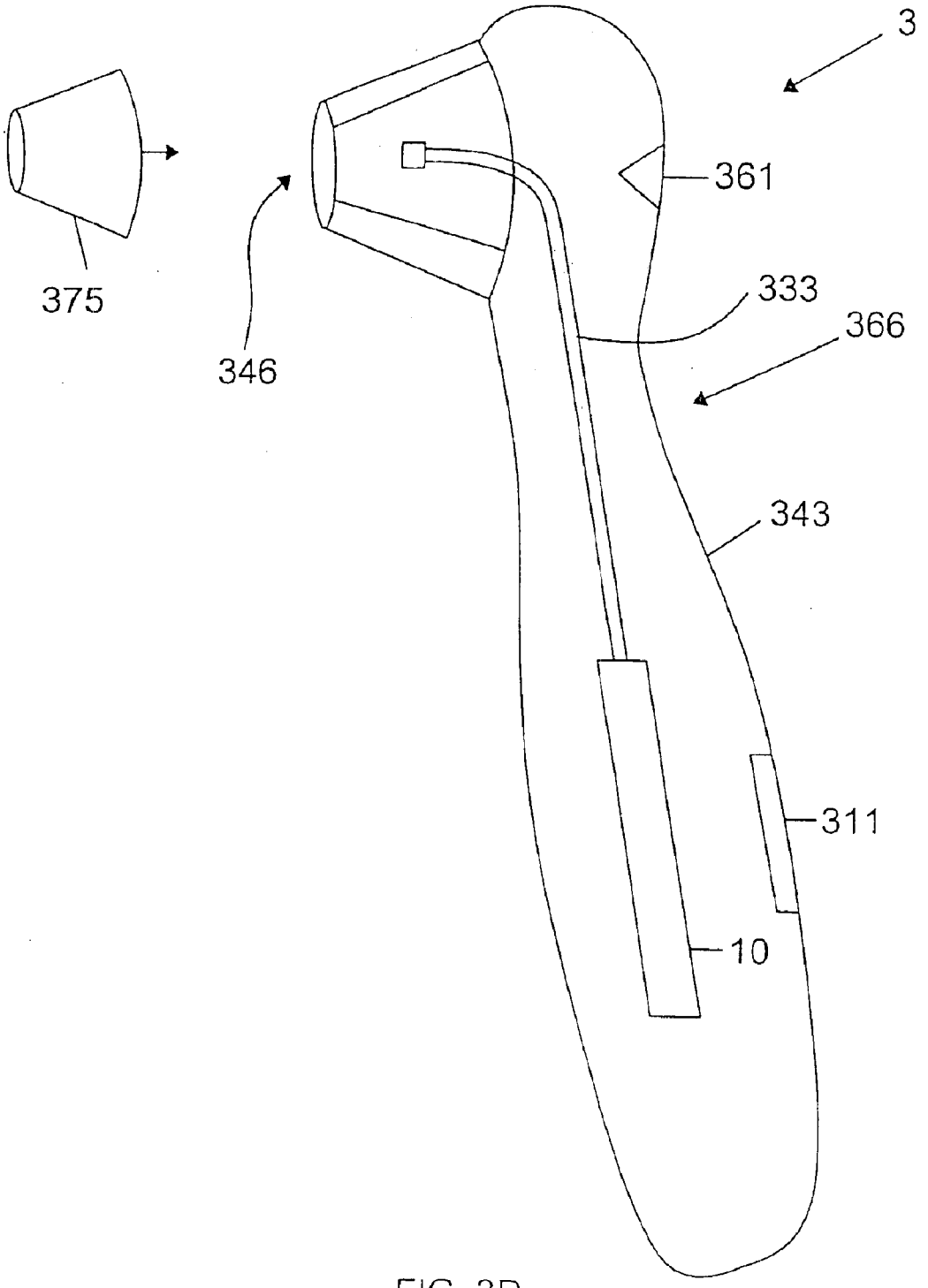

FIG. 3D

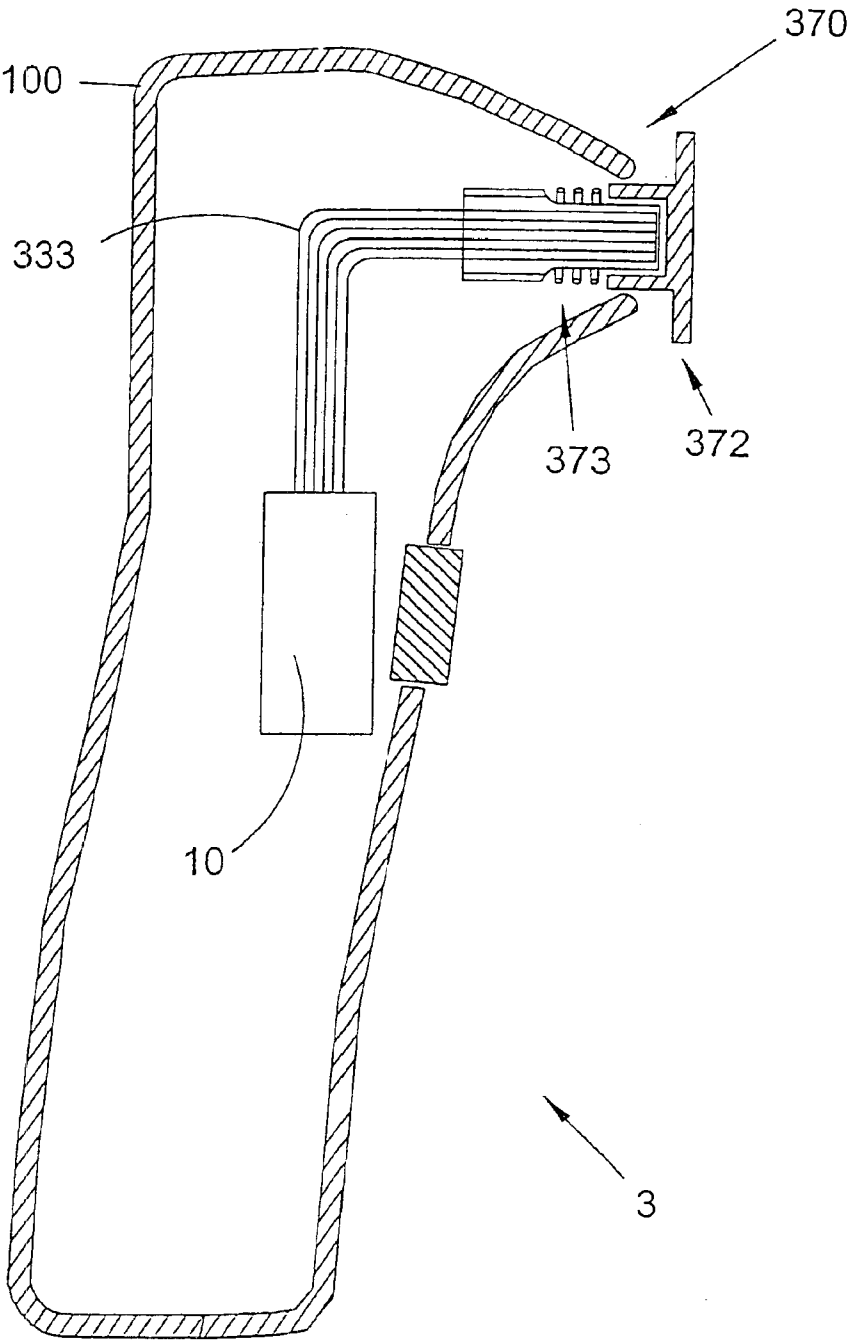

FIG. 3E

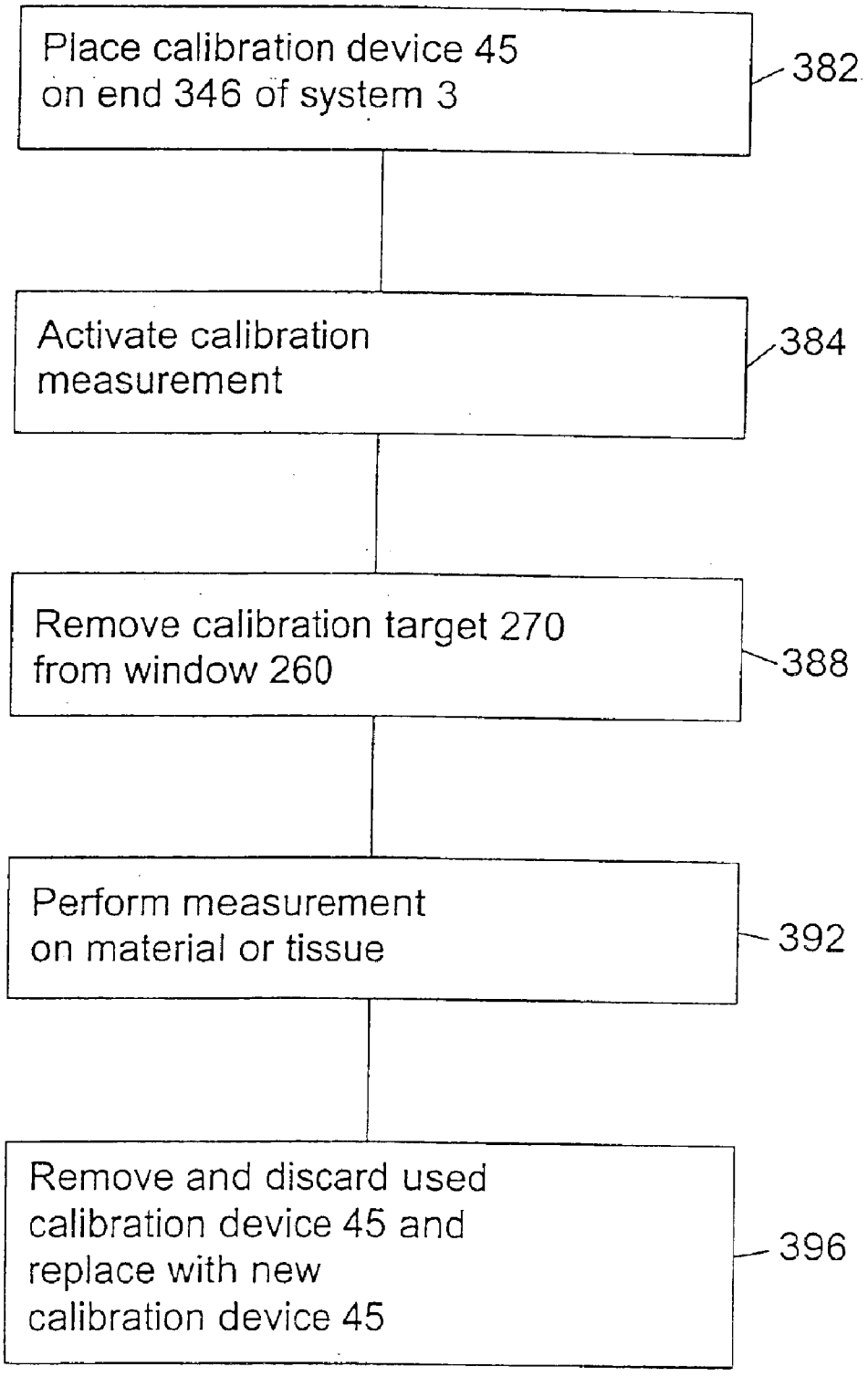
Place calibration device 45 on end 346 of system 3
382
Activate calibration measurement
384
Remove calibration target 270 from window 260
388
Perform measurement on material or tissue
392
Remove and discard used calibration device 45 and replace with new calibration device 45
396

FIG. 3F

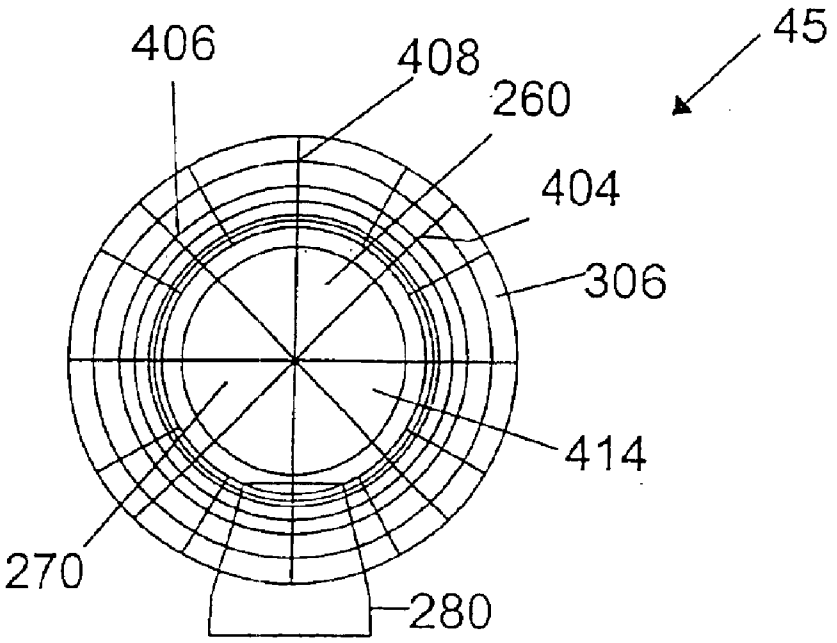

FIG. 4A

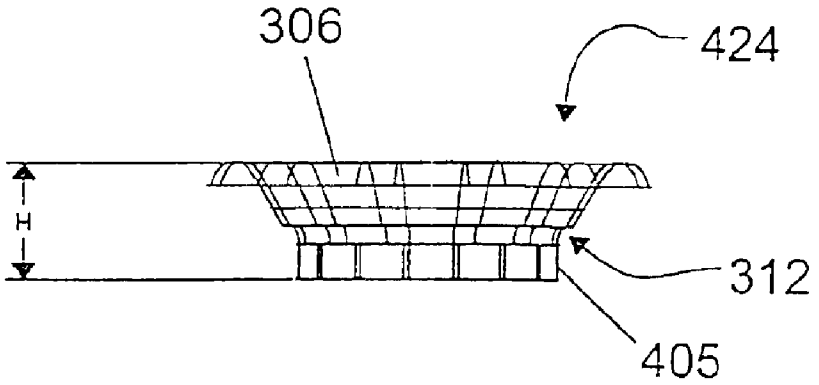

FIG. 4B

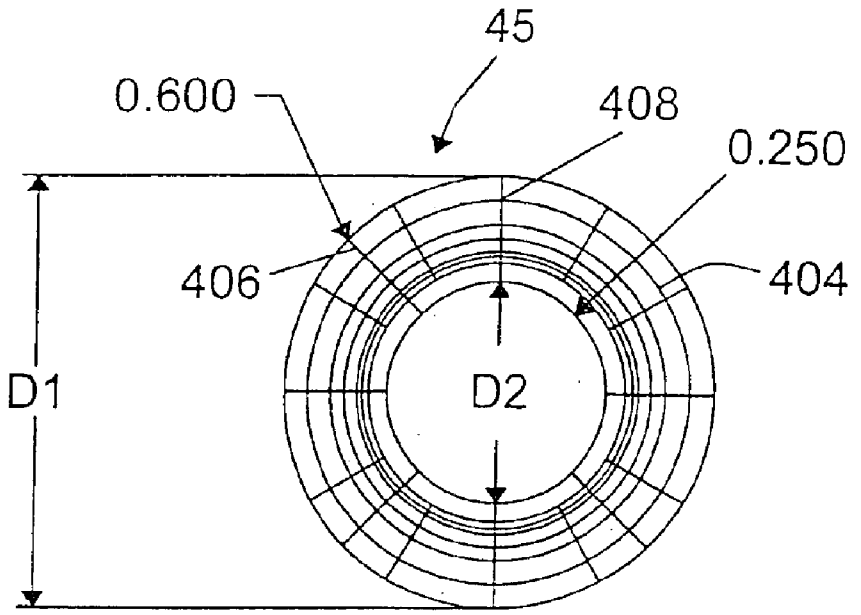

FIG. 4C

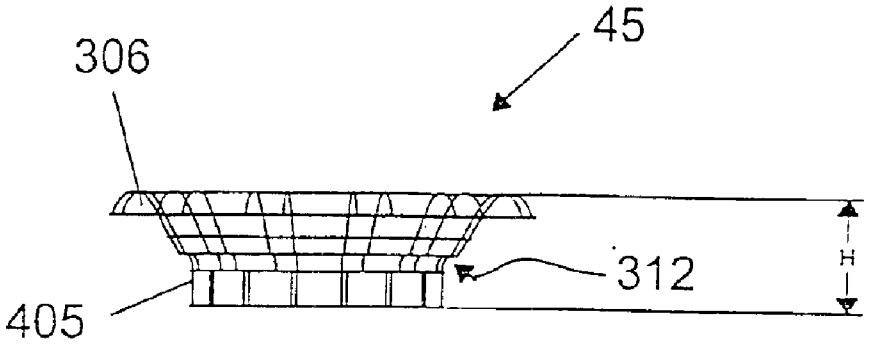

FIG. 4D

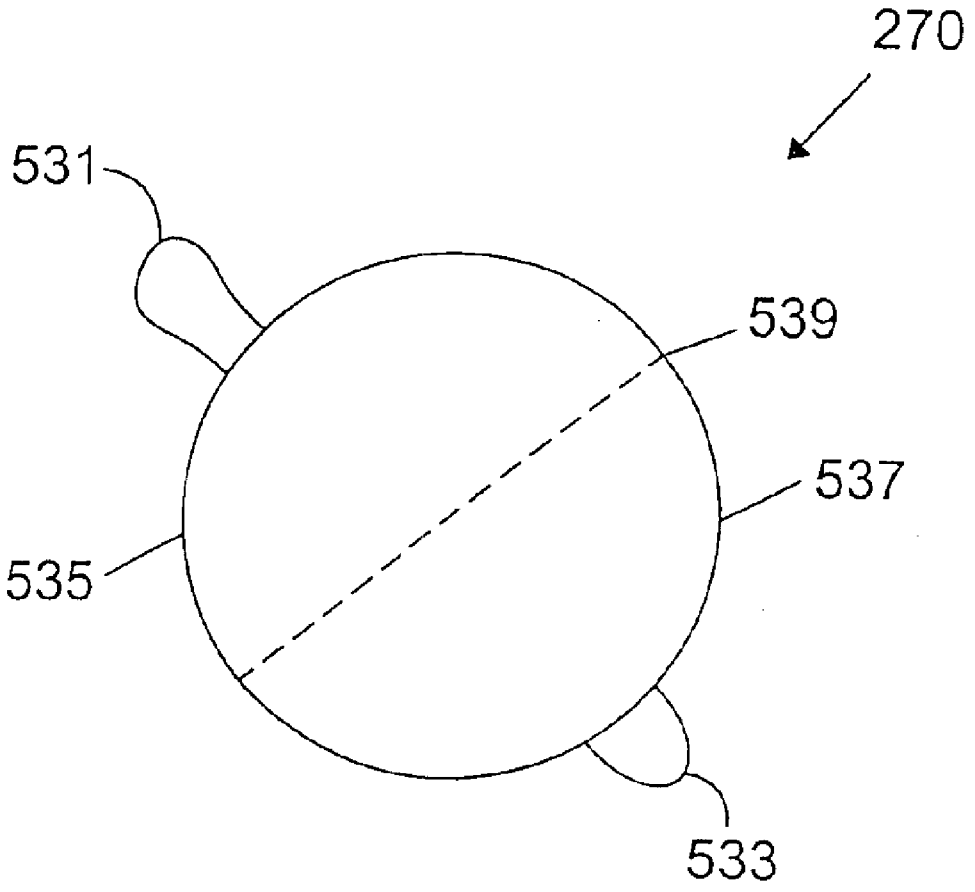

FIG. 4E

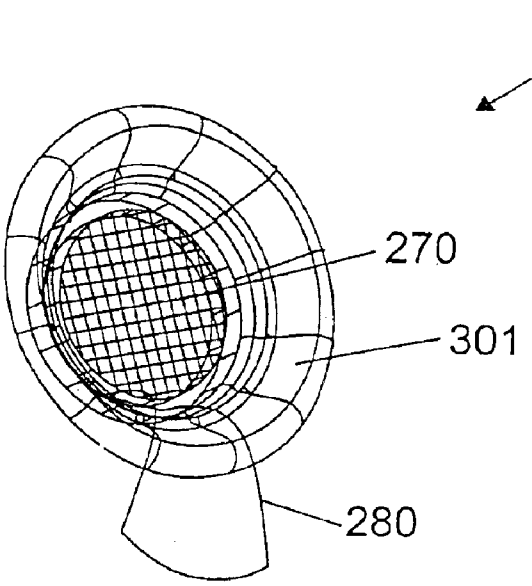

FIG. 5A

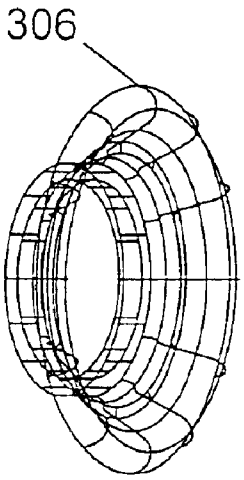

FIG. 5B

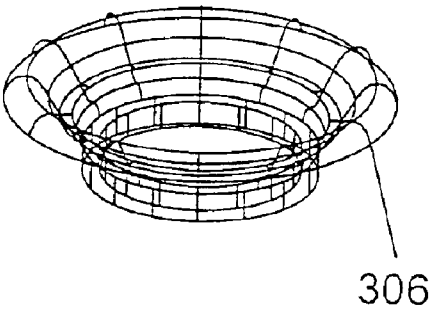

FIG. 5C

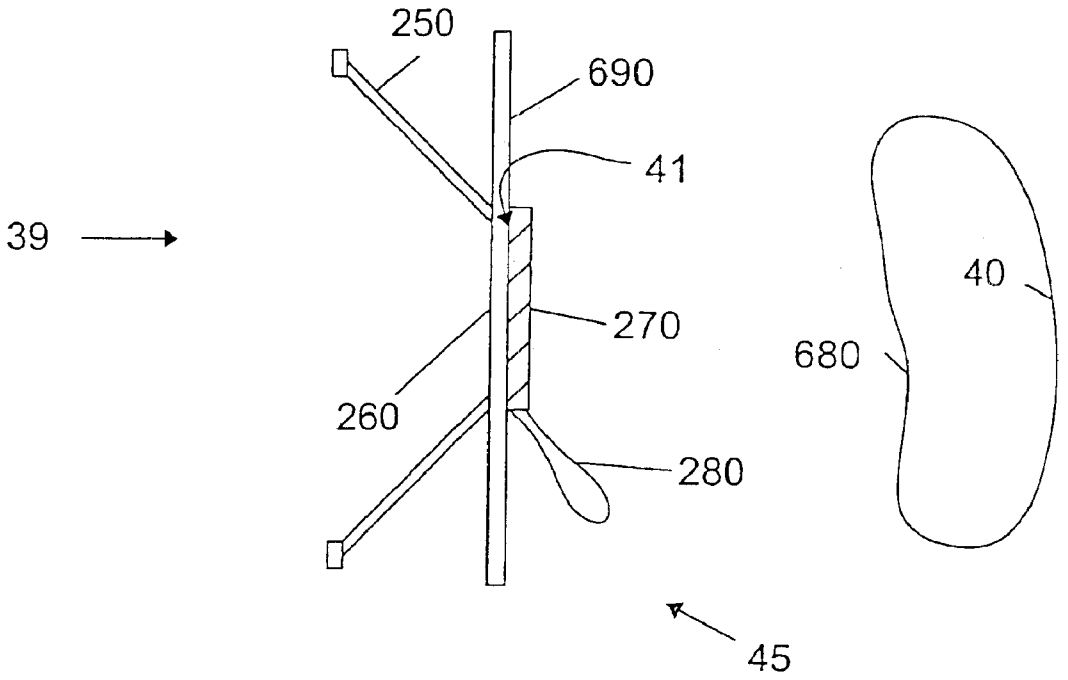

FIG. 6

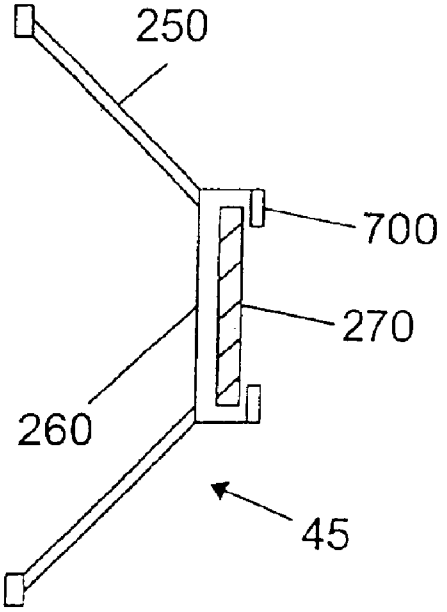

FIG. 7A

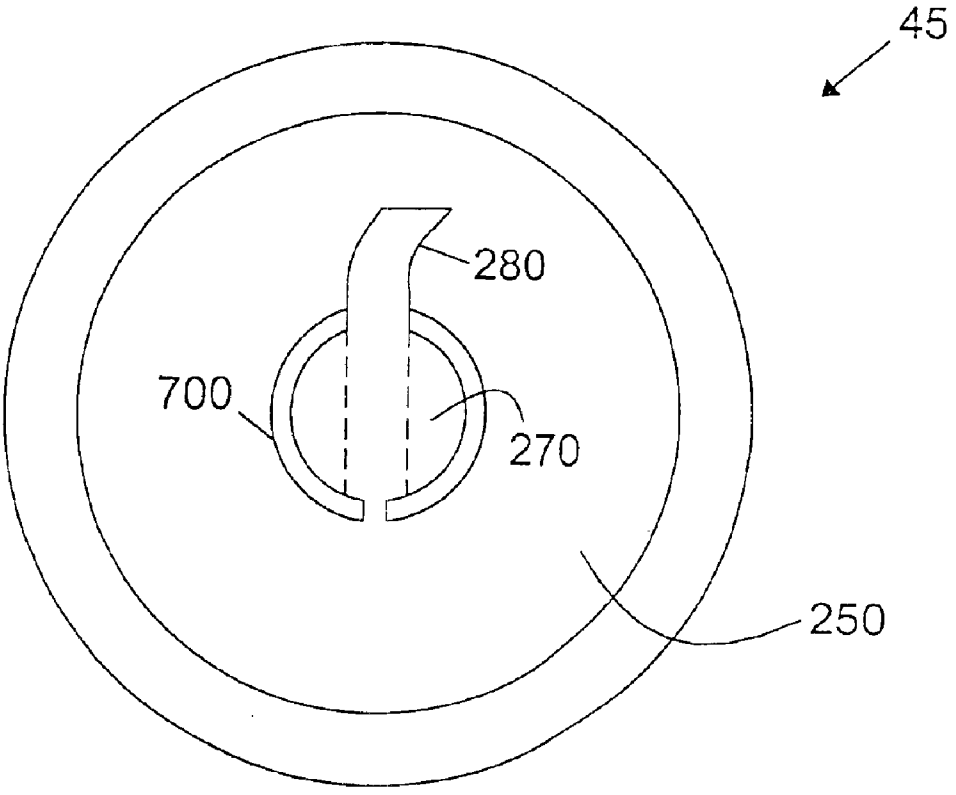

FIG. 7B

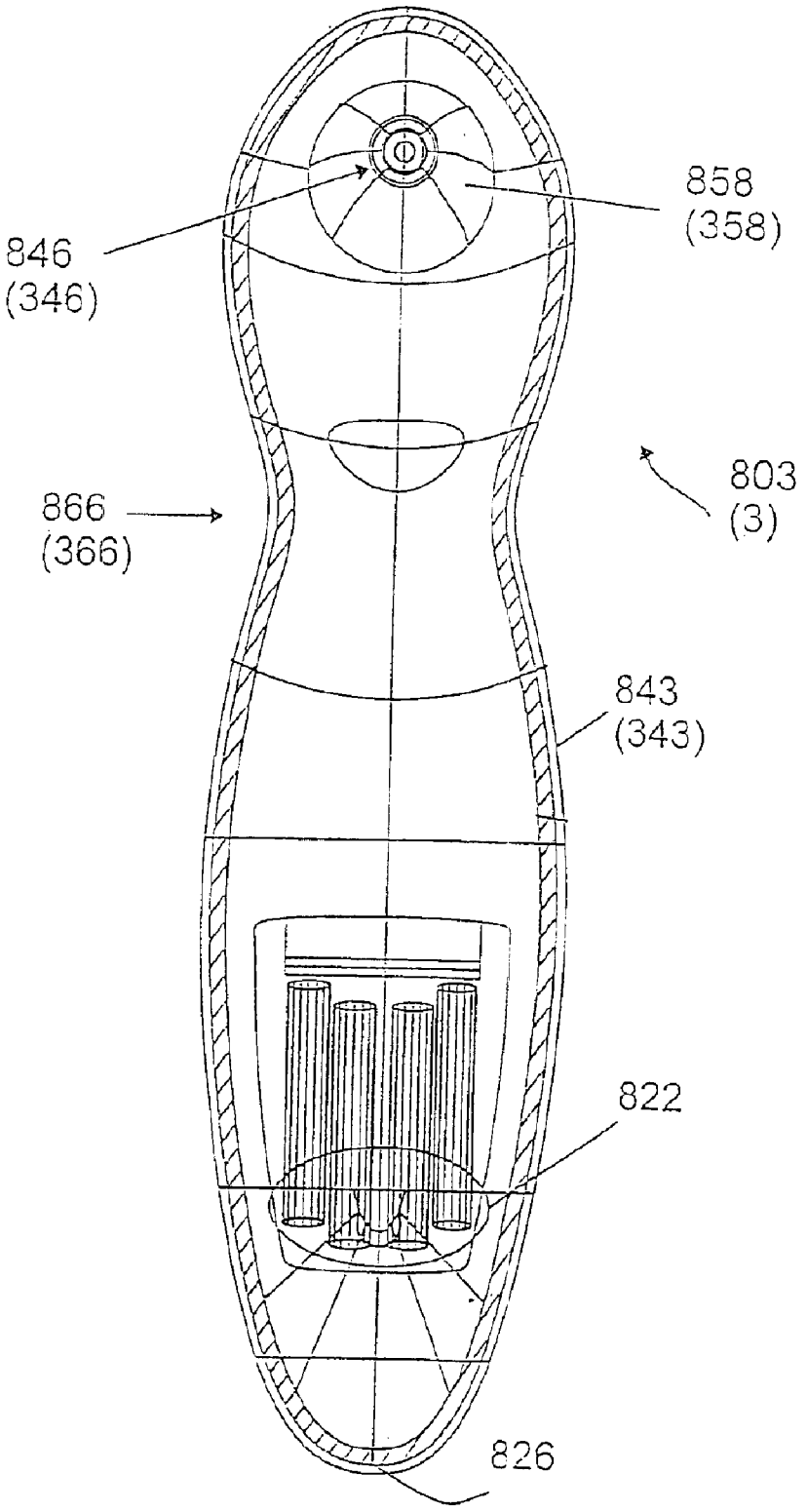

FIG. 8A

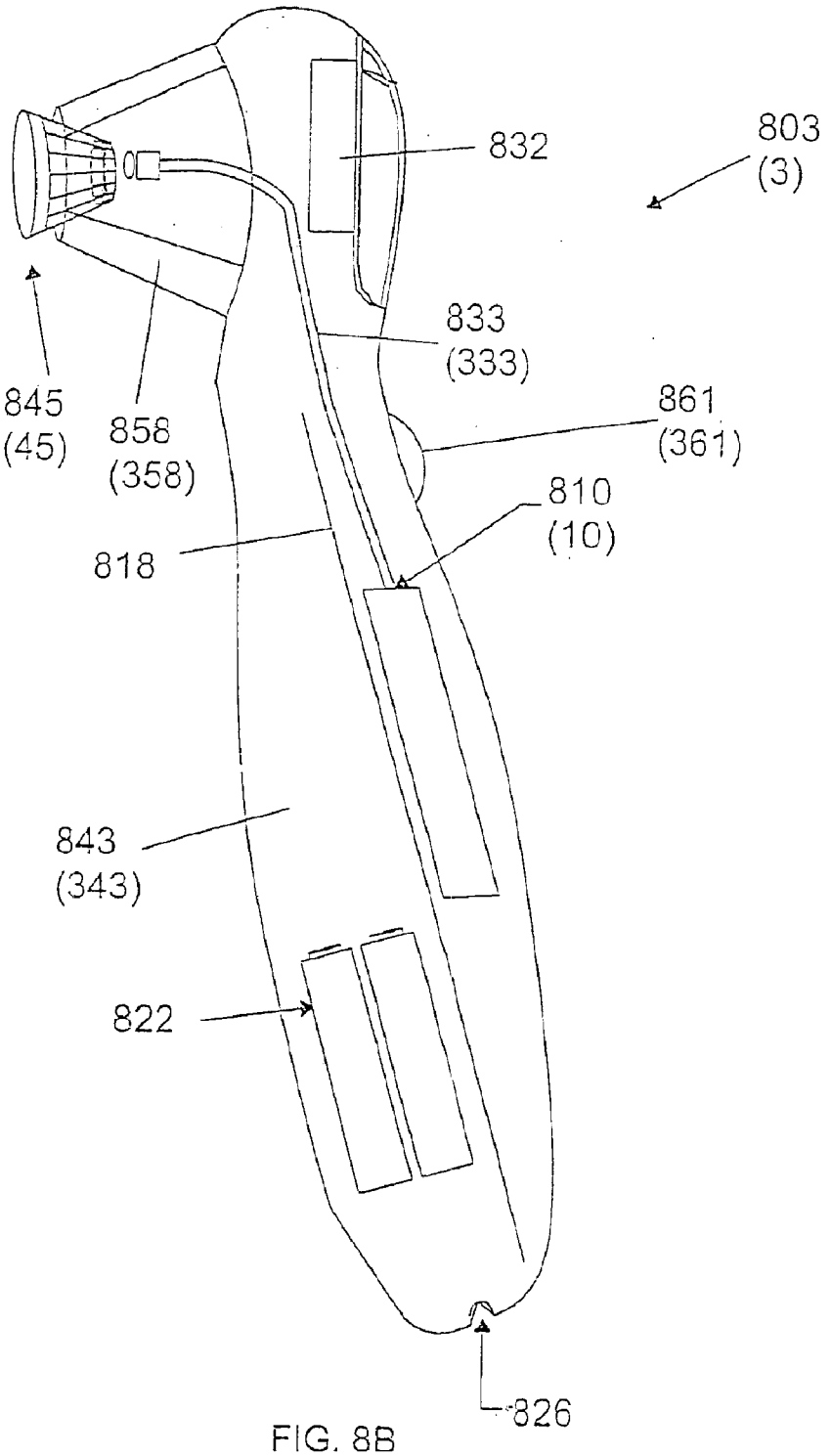
832
803
(3)
833
(333)
845
(45)
858
(358)
861
(361)
810
(10)
818
843
(343)
822
826

FIG. 8B

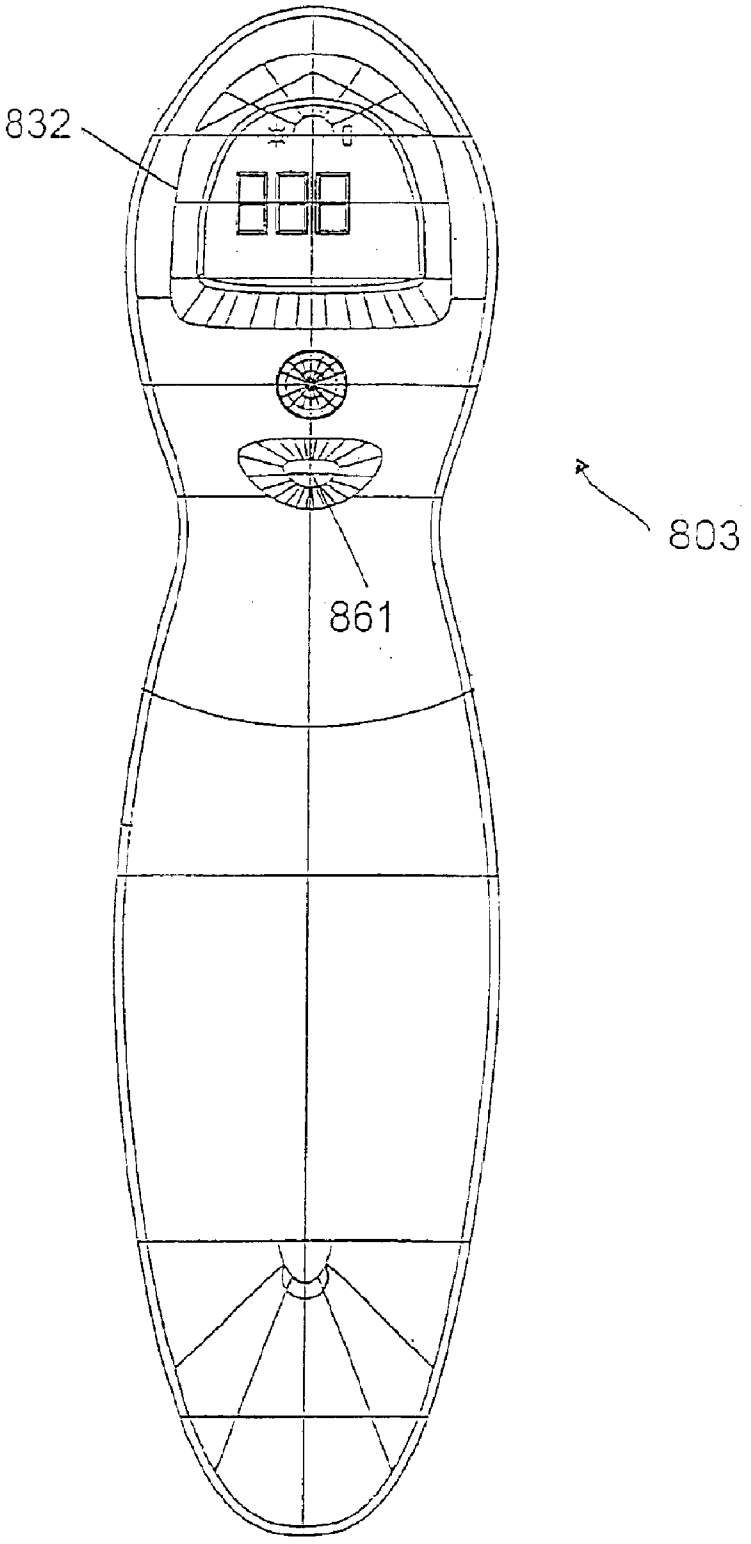

FIG. 8C

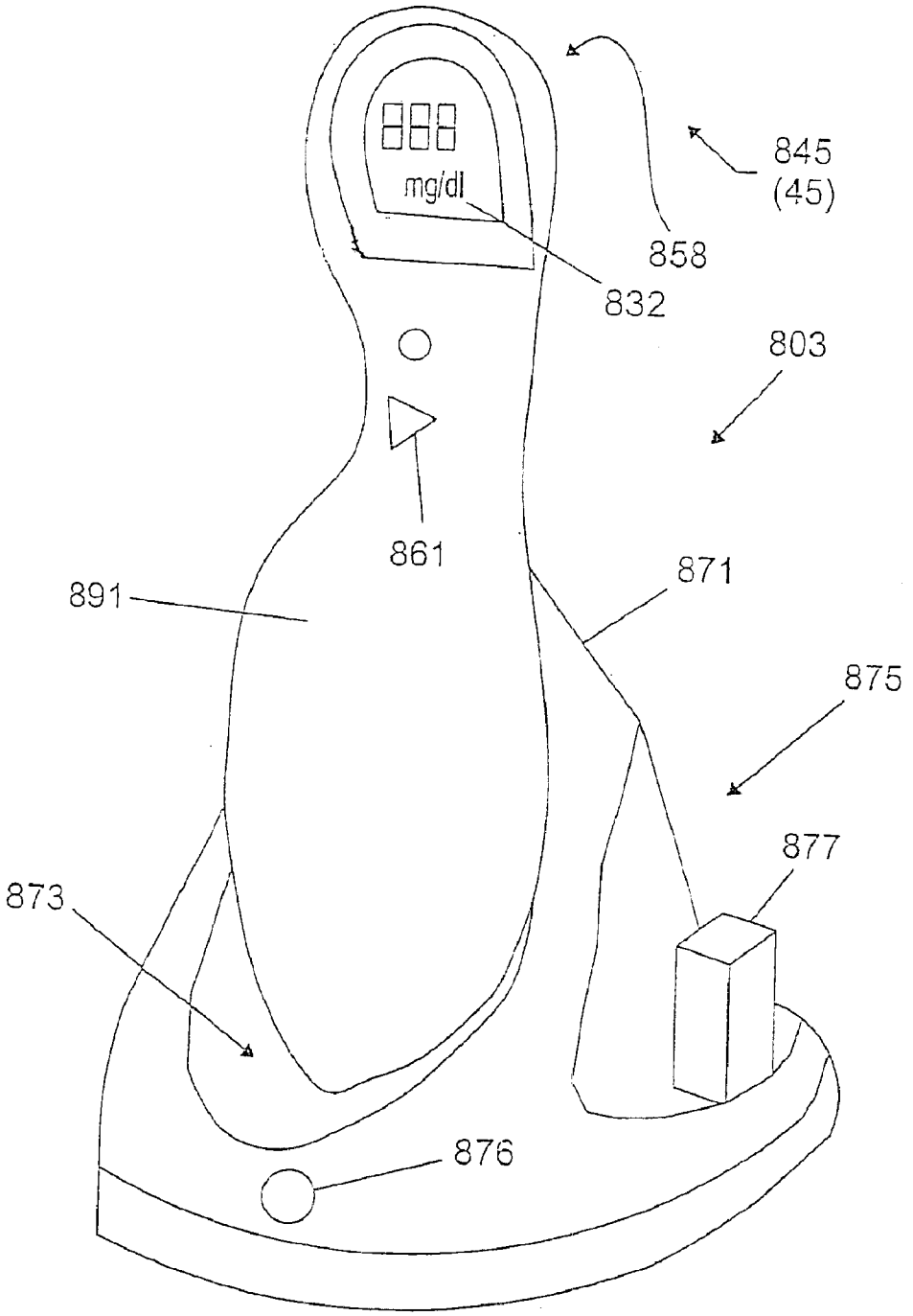

FIG. 8D

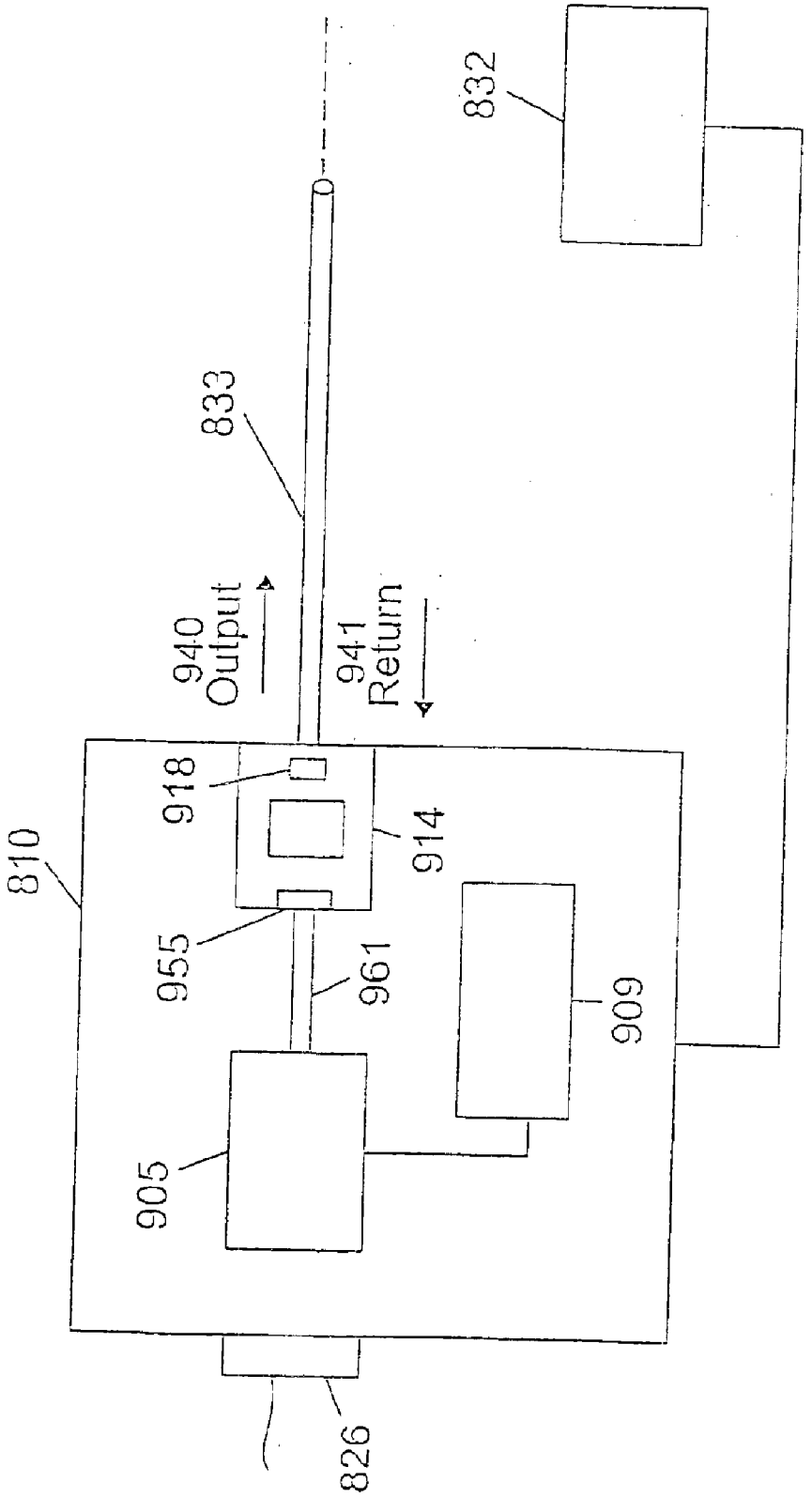

FIG. 9A

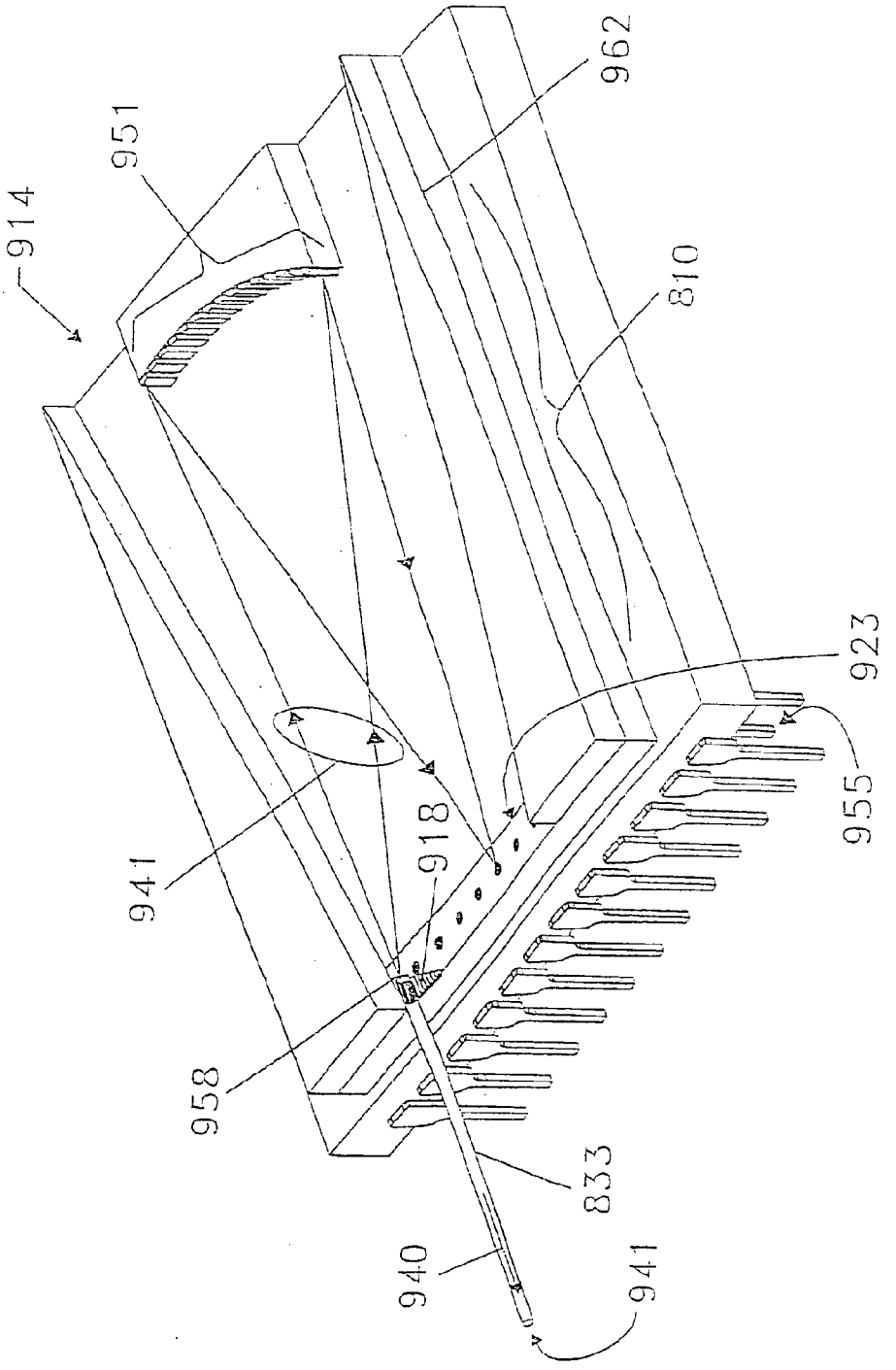

FIG. 9B

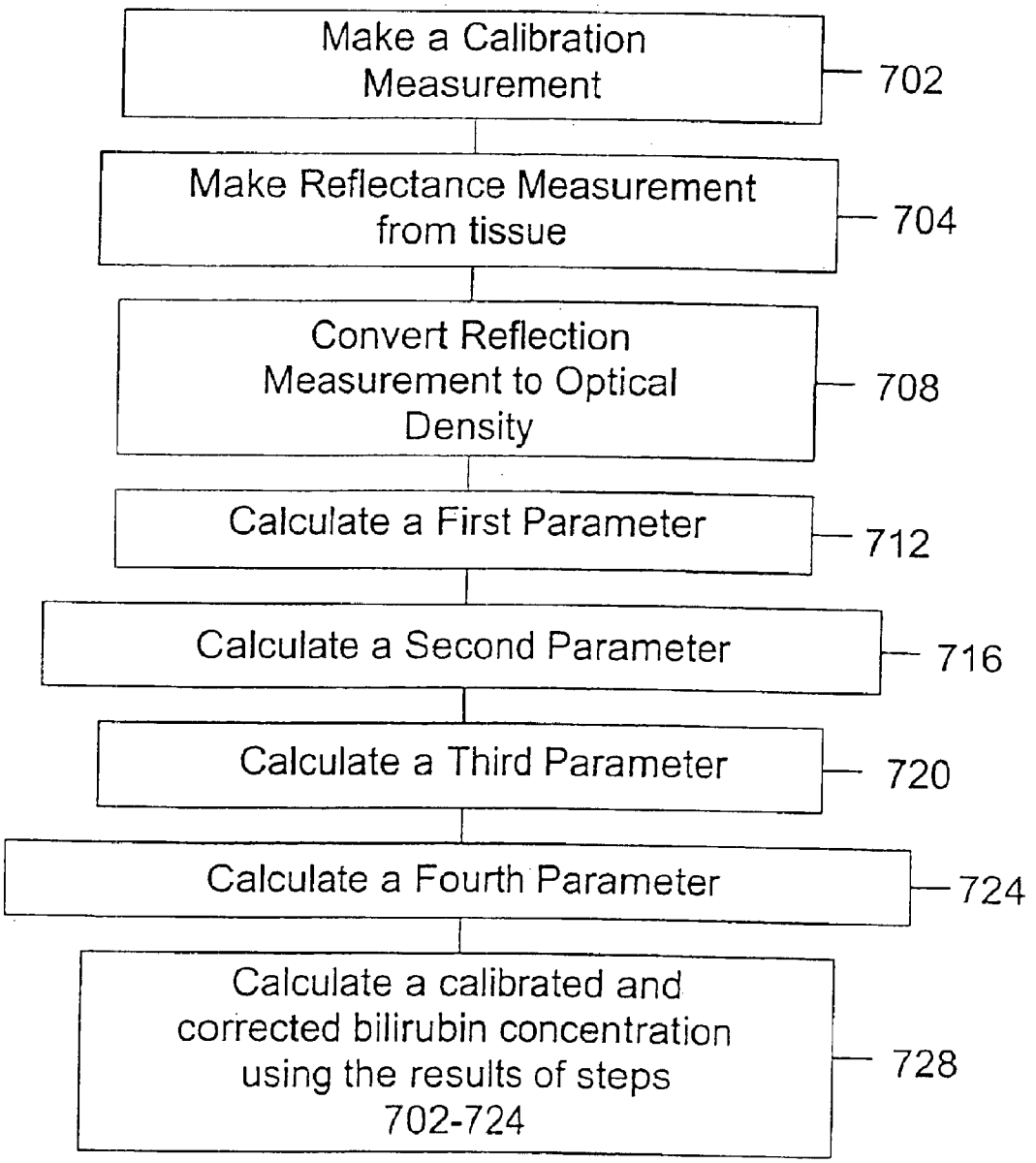
Make a Calibration Measurement
702
Make Reflectance Measurement from tissue
704
Convert Reflection Measurement to Optical Density
708
Calculate a First Parameter
712
Calculate a Second Parameter
716
Calculate a Third Parameter
720
Calculate a Fourth Parameter
724
Calculate a calibrated and corrected bilirubin concentration using the results of steps 702-724
728

FIG. 10

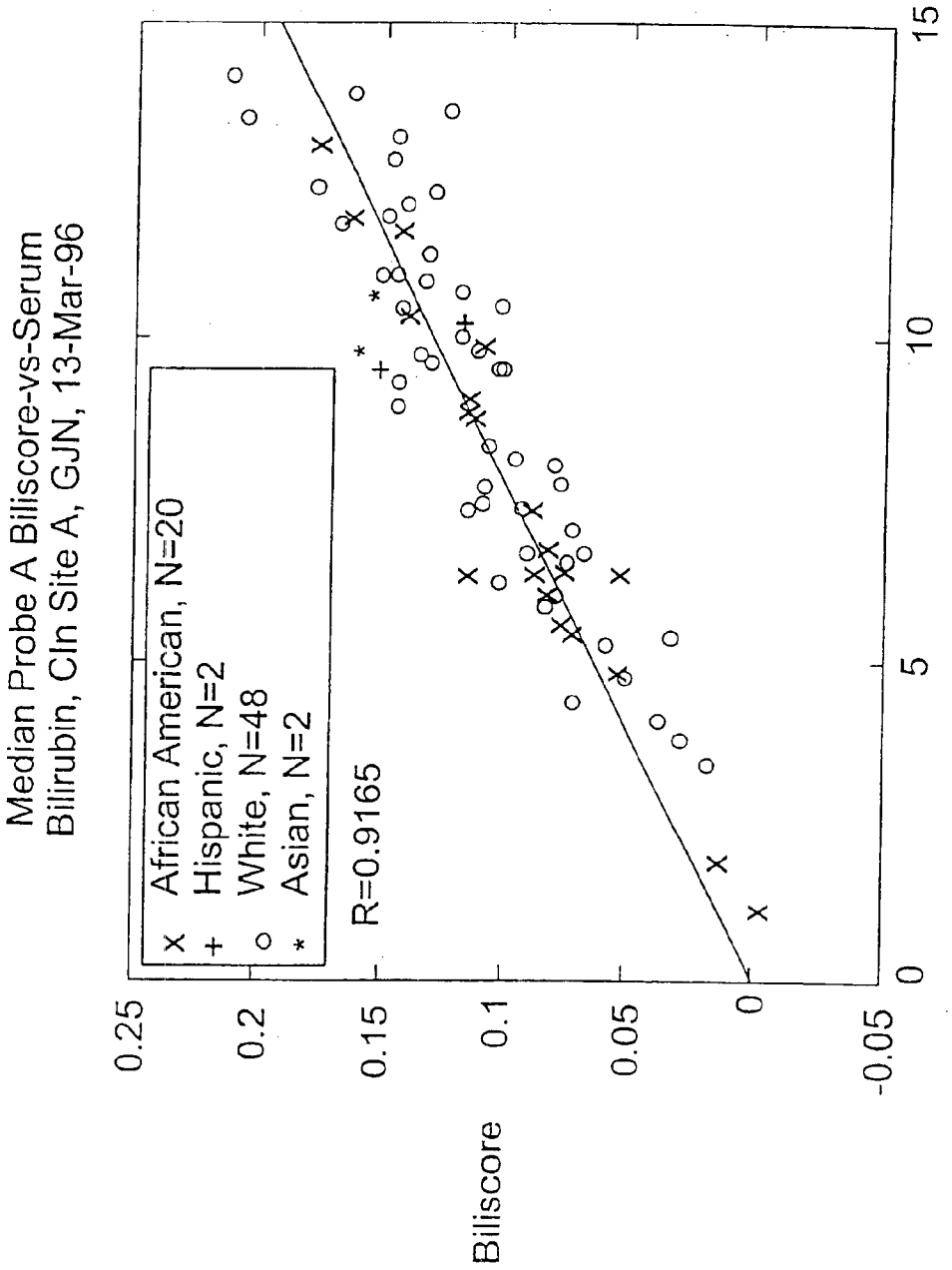
Median Probe A Biliscore-vs-Serum
Bilirubin, Cln Site A, GJN, 13-Mar-96
x African American, N=20
+ Hispanic, N=2
o White, N=48
* Asian, N=2
R=0.9165
Biliscore
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
5
10
15
Serum Bilirubin (mg/dl)

FIG. 11

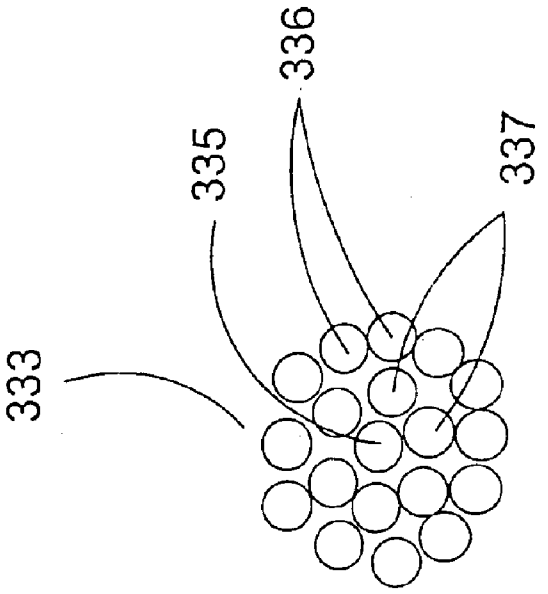

FIG. 13

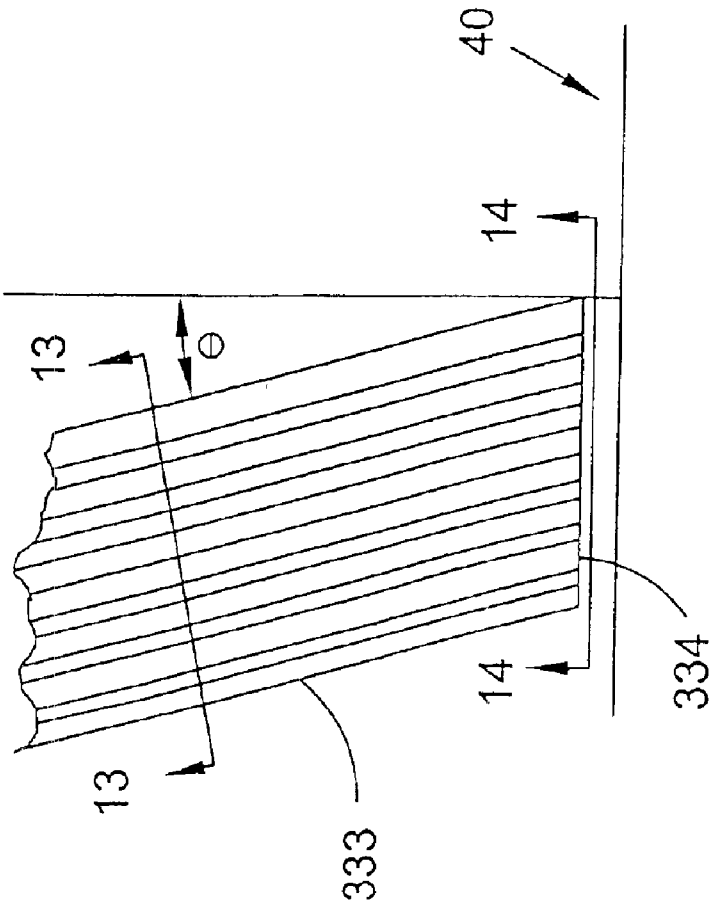

FIG. 12

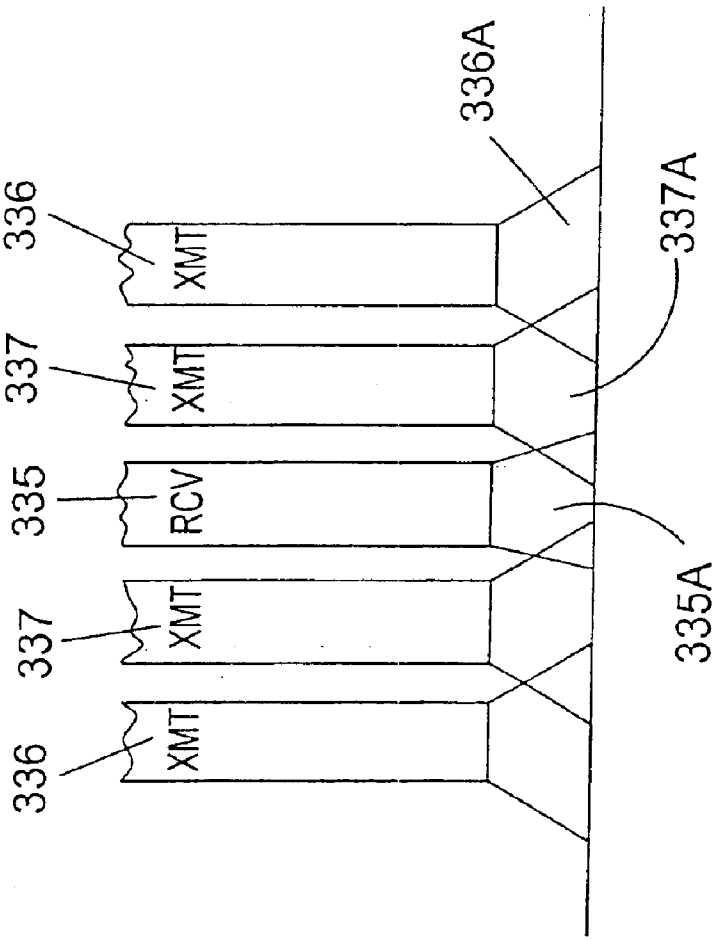
336
337
335
337
336
XMT
XMT
RCV
XMT
XMT
336A
337A
335A

FIG. 15

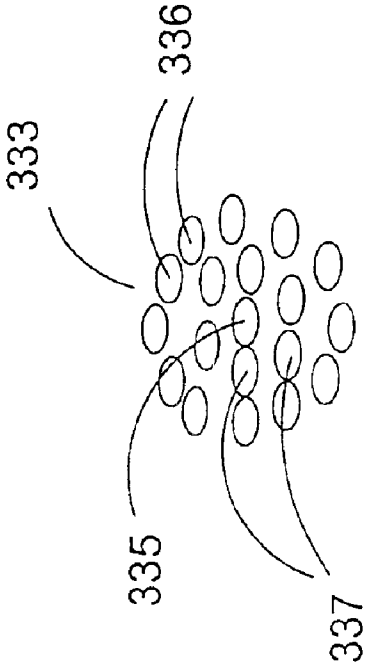
333
336
335
337

FIG. 14

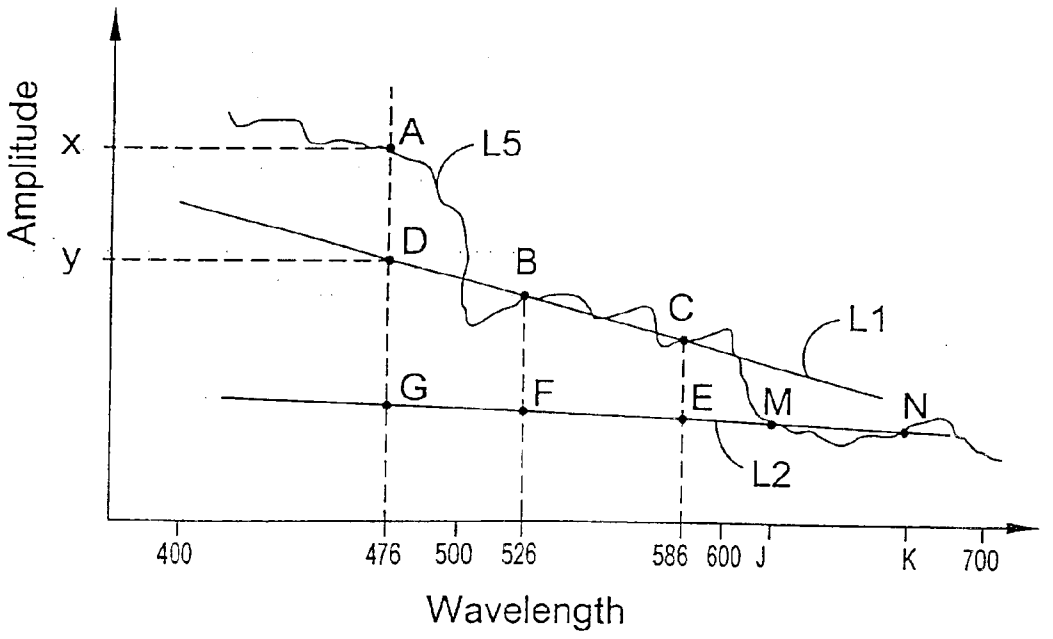
Amplitude
x
y
A
L5
D
B
C
L1
G
F
E
M
N
L2
400
476
500
526
586
600
J
K
700
Wavelength

FIG. 16

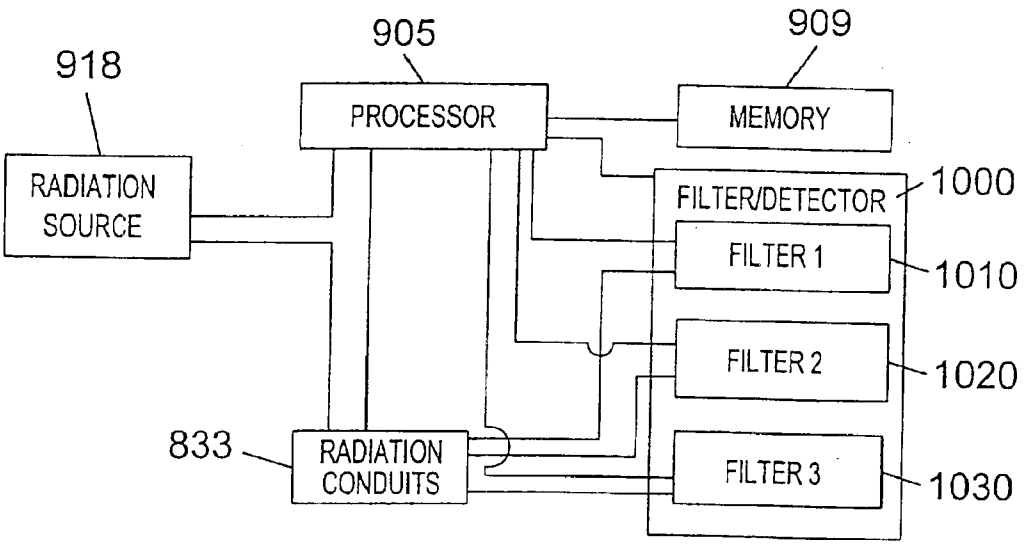
905
909
918
PROCESSOR
MEMORY
RADIATION SOURCE
FILTER/DETECTOR
1000
FILTER 1
1010
FILTER 2
1020
833
RADIATION CONDUITS
FILTER 3
1030

FIG. 17

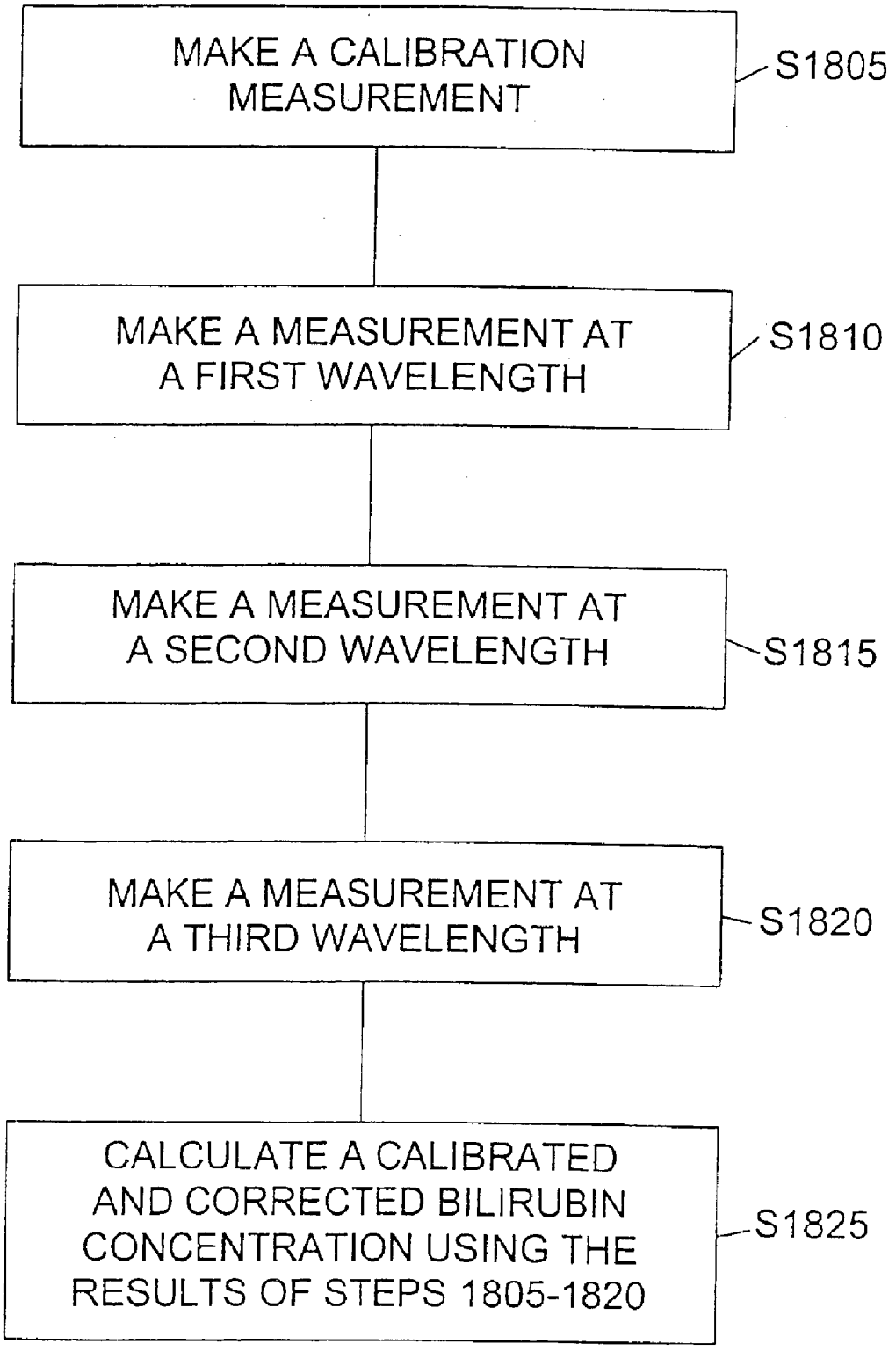
MAKE A CALIBRATION MEASUREMENT
S1805
MAKE A MEASUREMENT AT A FIRST WAVELENGTH
S1810
MAKE A MEASUREMENT AT A SECOND WAVELENGTH
S1815
MAKE A MEASUREMENT AT A THIRD WAVELENGTH
S1820
CALCULATE A CALIBRATED AND CORRECTED BILIRUBIN CONCENTRATION USING THE RESULTS OF STEPS 1805-1820
S1825

FIG. 18

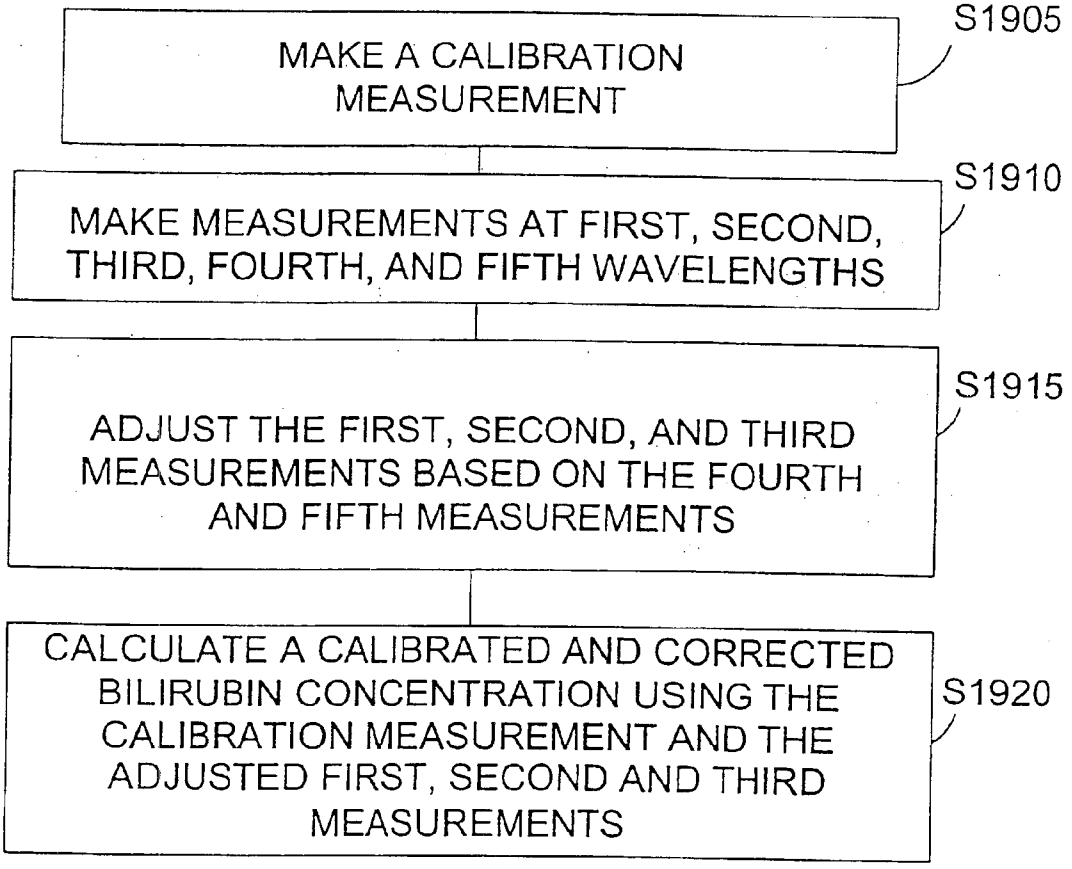
MAKE A CALIBRATION MEASUREMENT
S1905
MAKE MEASUREMENTS AT FIRST, SECOND, THIRD, FOURTH, AND FIFTH WAVELENGTHS
S1910
ADJUST THE FIRST, SECOND, AND THIRD MEASUREMENTS BASED ON THE FOURTH AND FIFTH MEASUREMENTS
S1915
CALCULATE A CALIBRATED AND CORRECTED BILIRUBIN CONCENTRATION USING THE CALIBRATION MEASUREMENT AND THE ADJUSTED FIRST, SECOND AND THIRD MEASUREMENTS
S1920

FIG. 19

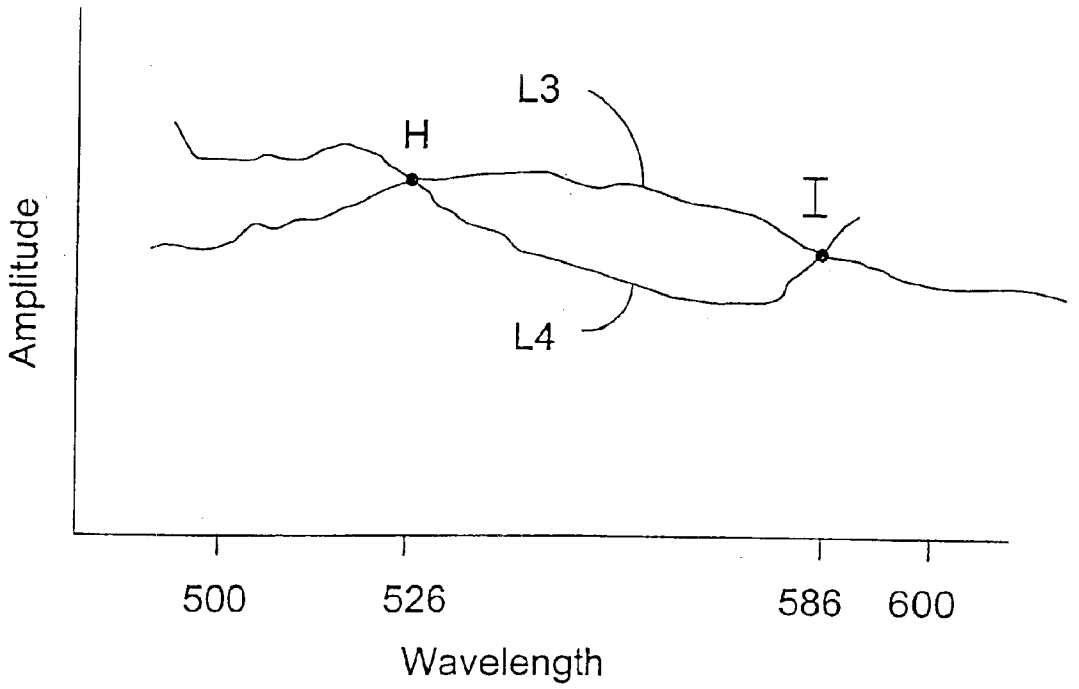

FIG. 20

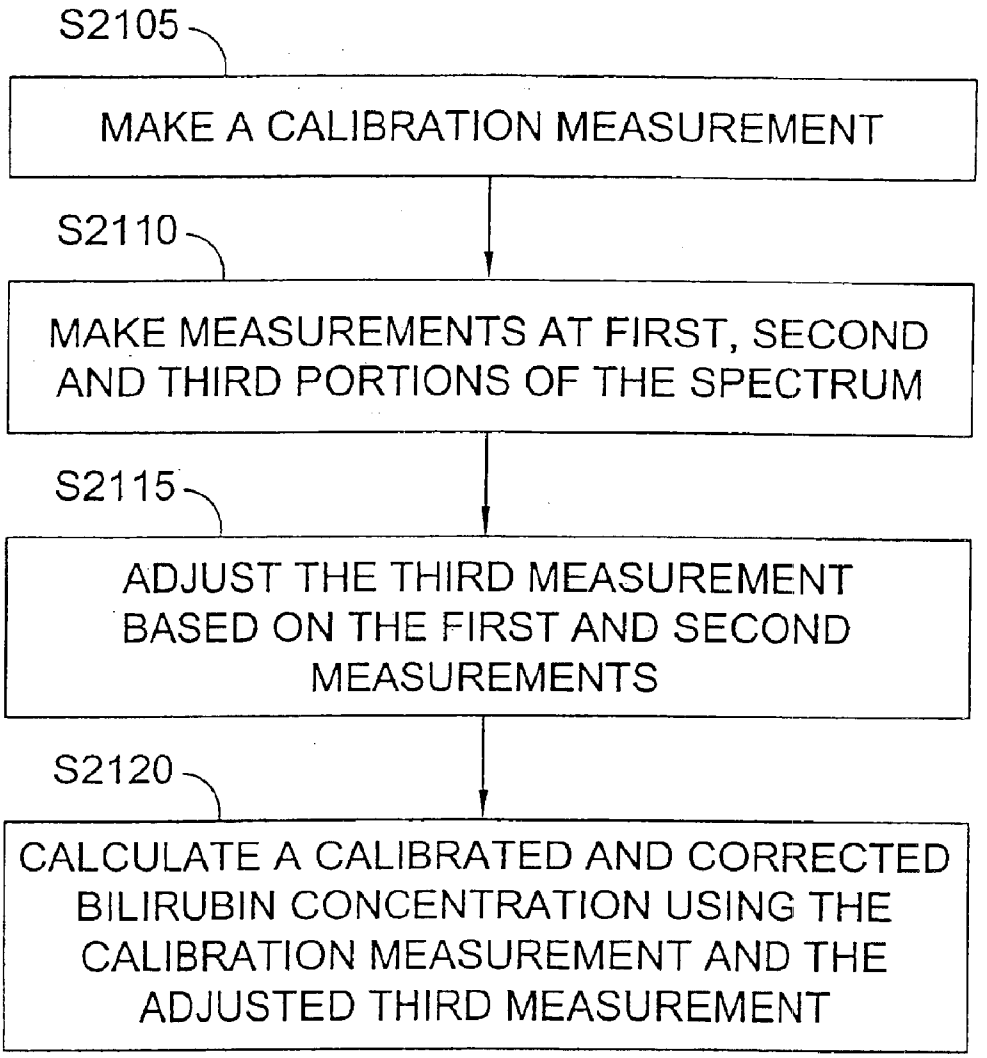
S2105
MAKE A CALIBRATION MEASUREMENT
S2110
MAKE MEASUREMENTS AT FIRST, SECOND AND THIRD PORTIONS OF THE SPECTRUM
S2115
ADJUST THE THIRD MEASUREMENT BASED ON THE FIRST AND SECOND MEASUREMENTS
S2120
CALCULATE A CALIBRATED AND CORRECTED BILIRUBIN CONCENTRATION USING THE CALIBRATION MEASUREMENT AND THE ADJUSTED THIRD MEASUREMENT

FIG. 21

METHOD AND SYSTEM FOR DETERMINING BILIRUBIN CONCENTRATION

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 09/589,403, filed Jun. 8, 2000 now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 09/286,649, filed on Apr. 6, 1999 now U.S. Pat. No. 6,192,734, which is in turn a continuation of U.S. patent application Ser. No. 09/054,490, filed on Apr. 3, 1998 now U.S. Pat. No. 5,924,981, which is in turn a continuation-in-part of U.S. patent application Ser. No. 08/904,766, filed on Aug. 1, 1997 now U.S. Pat. No. 6,045,502, which is in turn a continuation-in-part of U.S. patent application Ser. No. 08/621,182, filed Mar. 21, 1996 now abandoned, which in turn is a continuation-in-part of U.S. patent application Ser. No. 08/587,949, filed on Jan. 17, 1996 now U.S. Pat. No. 5,860,421. The contents of these applications are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to instruments that require calibration to make measurements on animal tissues or other materials, and in particular, to measurement instruments that utilize a removable calibration device that ensures proper calibration of the measurement instrument. The invention also relates to apparatus and methods of determining a bilirubin concentration in a human's blood.

2. Background of the Related Art

Spectroscopy is currently used for a wide variety of purposes including evaluation of in-vivo or in-vitro tissue samples. One type of spectroscopy, reflectance spectroscopy, involves diffusely reflecting light from tissue, non-invasively, and analyzing the reflected light. Such spectroscopic devices must be calibrated prior to use, especially when made for medical or other critical applications. Instrument calibration can be affected by variations in light source intensity, spectral characteristics, lens-aging, lens cleanliness, temperature, detector sensitivity changes, and electronic drifting.

More generally, there has been an increase in the use of light as a diagnostic tool in many areas of medicine. This development has become more pervasive with the development of appropriate and inexpensive light sources, detection devices and optical fibers that allow for minimal invasiveness.

Typically, spectral transmittance, fluorescence (normal and time resolved) and Raman spectroscopy are used to evaluate biological tissues and other materials in order to determine the materials present and to measure their concentrations. These methods are affected by the scattering, reflecting, absorbing and transmitting properties of the instrument optics, detectors, sources and the media under examination. This is due to the fact that the amount of light reaching the tissue to be measured is a function of those parameters, and in the case of fluorescence and Raman emissions, re-absorption of emission spectra.

Acoustic type measuring systems are also used for a wide variety of purposes including to evaluate tissue or materials. Acoustic measurement systems also experience variations in the output energy of the acoustic wave source, changes in spectral characteristics of the tissue or material due to changes in temperature, detector sensitivity changes, and electronic drifting.

Many of the above-described types of measurement systems require calibrations to be performed on a routine basis in order to compensate for changes in instrument performance and response. This is true for both radiation based measurement systems, i.e., systems that reflect electromagnetic radiation from the tissue or material to be measured and then analyze the return radiation, and acoustic based measurement systems, i.e., systems that reflect acoustic waves or energy from the tissue or material to be measured and then analyze the return acoustic signal.

Calibration techniques typically involve measuring the response of a test target with characteristics that remain stable over time and over a range of temperatures. Those calibration techniques can also be used to compensate for instrument to instrument variations, and for any changes that an individual instrument may experience over its working lifetime.

Although others have proposed calibration fixtures that compensate for these variations in instrument performance, none have provided a simultaneous solution to both the calibration issue and the problems associated with the spread of infection in a medical setting. Furthermore, calibration devices that are designed to be reused can become damaged by sunlight, temperature, humidity and other effects, which could lead to errors in calibration.

Various types of calibration techniques and devices have been attempted. For example, U.S. Pat. No. 5,365,925 describes a calibration boot which includes a plurality of materials, which is placed over an optical catheter for the purpose of making a multi-point calibration of reflected or backscattered light. U.S. Pat. No. 5,311,273 describes a method of using four black body radiators to provide calibration of an infrared spectrometer. However, neither of these approaches involves an inexpensive calibration target that can be easily discarded after each use. In addition, neither of these systems prevent a user from taking a measurement without going through a calibration step.

U.S. Pat. No. 4,981,355 describes a calibration device for the in vitro calibration of a light guide, whereby a polyethylene material has a plurality of light scattering particles and a plurality of light absorbing particles which yields a neutral density filtering type of effect, uniformly distributing light in the plastic parts of the calibrator. The calibrator can be positioned into a sterile tray which is protected by a tear off plastic. Once the calibration is complete, the surgeon removes the catheter from the calibrator and the tray in which it is held and then presumably disposes of the calibration device and its tray. This approach, however, is neither simple nor inexpensive.

U.S. Pat. No. 4,796,633 describes a calibration reference apparatus that fits over a light guide. A stop limits the extent to which the light guide can be advanced into the cavity, whereby an endface of the light guide is spaced from a region of the surface to define a gap. The end wall and the gap are adapted to return a known ratio of the light directed into the gap from the end face of the light guide. Again, however, this approach does not involve an inexpensive, disposable calibration device.

U.S. Pat. No. 4,744,656 discloses a calibration boot that snaps into place over an optical catheter allowing calibration of the catheter before use. Once the calibration is complete, the boot is removed and the optical catheter is ready for use. Each new catheter comes with a new boot. However, the boot is not present during the measurement and there is no provision to prevent reuse of the boot.

One application of spectroscopic systems involves detection of a bilirubin concentration in a human. Bilirubin is

produced from the breakdown of hemoglobin in red blood cells. Under normal conditions, the bilirubin is conjugated by glucoronyl transferase, an enzyme present in the liver, and is then excreted through the biliary system.

Newborn infants and prematurely born infants are particularly susceptible to hyperbilirubinemia. Hyperbilirubinemia describes the state where there is excessive bilirubin in the body. Often this is due to the lack of functioning glucoronyl transferase enzyme in their liver, or excessive red blood cell breakdown associated with erythroblastosis fetalis.

One method for bilirubin testing includes blood based lab assay testing. The "heel stick" blood lab assay is currently the only accepted methodology for quantitative bilirubin testing results in the United States. Of course, this invasive approach requires that blood be drawn to perform the test.

Non-invasive measurements of the bilirubin concentration would eliminate the need to draw blood samples from patients for bilirubin analysis. It would also provide easy patient interface. It is known that bilirubin can be measured non-invasively by taking reflectance measurements from a patient's skin, from the aqueous of the eye, or from the sclera (white) of the eye, based on the fluorescent signature. Reflectance measurements can also be made on the tympanic membrane of the ear. This is possible because bilirubin from the blood stains the skin as well as other tissues of the body. Jaundice refers to the condition when the bilirubin is visible in the skin and sclera.

Many attempts have been made to measure cutaneous bilirubin non-invasively. These attempts include the development of visual reference standards, and transcutaneous reflectance spectroscopy to measure the absorption spectra of bilirubin, oxidized blood, and melanin, the dominant absorbers in the skin. The concentration of these pigments have distinct absorption spectra.

Reflectance bilirubinometers have obtained reasonable correlations between bilirubin levels determined transcutaneously and serum bilirubin concentrations in homogeneous patient populations. Unfortunately, these devices have failed to give satisfactory correlations when used over a heterogeneous population. Since patient populations are rarely homogeneous, transcutaneous bilirubin measuring methods have not been widely accepted clinically.

One known system, which implements a non-invasive cutaneous testing approach for bilirubin and is in wide use in Japan, is the Minolta Jaundice Meter. That approach, however, has not been approved for use in the United States, although it is used for screening purposes in some U.S. institutions. In addition, that approach does not account for variations in skin color and thickness.

Another approach to testing for bilirubin that does not require the drawing of blood is a breath analysis approach introduced by a group from Stanford. This approach does not have a quantitative accuracy required to have a high correlation to serum bilirubin. Hence, it appears to only have potential use as a screening technique.

SUMMARY OF THE INVENTION

An object of the invention is to provide a simple and accurate apparatus and method of measuring a patient's bilirubin concentration.

A measurement instrument embodying the invention, that utilizes electromagnetic radiation, may include one or more transmit and receive fiber optic waveguides for directing electromagnetic radiation to a material or tissue to be measured and for conducting reflected or dispersed radiation back to a sensor of the instrument. The instrument may be configured such that radiation transmitted from the instrument toward the material or tissue being measured is directed toward the material or tissue at an angle relative to a plane normal to the surface of the material or tissue so as to reduce backscattering effects.

Another feature of the invention is that a calibration device embodying the invention may include an index matching substance, such as a gel, that can be interposed between a material or tissue being measured and a distal end of a measurement instrument.

Another feature of the invention is that a measurement instrument designed to measure a bilirubin concentration in a patient may accomplish the measurement using the amplitude of radiation reflected from a patient's skin at first and second wavelengths representing a blood content of the skin, and at a third wavelength representing an uncorrected bilirubin concentration. Such an instrument may also utilize the amplitude of reflected radiation at fourth and fifth wavelengths that represent a melanin content of the patient's skin.

A measuring instrument embodying the invention may include a radiation analyzer that transmits radiation to a material or tissue in order to effect measurements and that receives and analyzes radiation reflected from or dispersed from a material or tissue being measured. Alternatively, an instrument embodying the invention may emit, receive and analyze acoustic energy. The instrument may include a calibration device holder for holding a calibration device that includes a structure through which the radiation or acoustic energy can be transmitted, and that includes a removable calibration target arranged on said structure and capable of returning a portion of said radiation or acoustic energy for calibrating the instrument. The removable calibration target is removable from said structure to allow a measurement to be made on a material or tissue.

A measuring instrument embodying the invention may comprise a spectrometer capable of determining the amplitude of radiation at any of a plurality of wavelengths. Alternatively, the measuring instrument may comprise a detector and one or more filters for selectively focusing radiation of specified wavelengths upon the detector. The measuring instrument could also comprise a plurality of filters and a corresponding plurality of detectors, where reflected radiation passes through the filters and onto the detectors so that each detector receives radiation at a different wavelength. The measuring instrument might also comprise a diffraction grating and a plurality of detectors, wherein the diffraction grating focuses radiation of predetermined wavelengths on respective ones of the plurality of detectors. Still further, the radiation analyzer may comprise a radiation detector and a linear variable filter.

A method of determining a bilirubin concentration of a patient that embodies the invention can include measuring the amplitude of reflected radiation at first and second wavelengths to determine a blood content of the patient's skin, measuring an amplitude of radiation at a third wavelength to determine an uncorrected bilirubin concentration of the patient, and analyzing the data to determine a corrected bilirubin concentration. A method embodying the invention may also include the step of measuring the amplitude of reflected radiation at fourth and fifth wavelengths to determine a melanin concentration in the patient's skin and analyzing the amplitudes of the first, second and third frequencies in light of the detected melanin concentration.

Another method of determining a bilirubin concentration of a patient that embodies the invention can include illumi-

nating a portion of a skin of the mammal with light, detecting a frequency spectrum of light scattered from the skin, determining, from first and second portions of the spectrum, a first parameter indicative of a blood oxygen content of the skin and a second parameter indicative of melanin content of the skin and scattering, determining, from a third portion of the spectrum, a third parameter indicative of an uncorrected bilirubin concentration, and calculating a corrected bilirubin concentration based on the first, second and third parameters

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows a schematic view of a measurement system in a calibration mode;

FIG. **1**B shows a measurement system in a measurement mode wherein a calibration target has been removed and radiation is reaching a tissue or material to be measured;

FIG. **2**A shows a schematic representation of an embodiment of a calibration device for use with a measurement instrument;

FIG. **2**B shows the calibration device of FIG. **2**A after a calibration target is removed (peeled) from a window of the device;

FIG. **2**C shows a schematic sectional representation of another calibration device for use with the measurement instrument;

FIG. **2**D is a schematic representation of the calibration device of FIG. **2**C wherein a removable seal has been peeled away from the calibration device;

FIG. **2**E shows a schematic representation of the calibration of FIG. **2**C mounted on a measurement instrument wherein a calibration target has been removed;

FIG. **2**F is a schematic sectional representation of yet another embodiment of the calibration device for use with the measurement instrument;

FIG. **2**G shows the calibration device of FIG. **2**F mounted on a measurement instrument wherein a removable calibration target has been peeled away from the device;

FIG. **3**A is a schematic representation of yet another embodiment of a calibration device for use with a measurement instrument;

FIG. **3**B is a schematic representation of the calibration device of FIG. **3**A positioned adjacent a material or tissue to be measured with a calibration target partially removed from the device;

FIG. **3**C shows a measurement system which utilizes a disposable calibration device as shown in FIGS. **3**A and **3**B;

FIG. **3**D shows the measurement system of FIG. **3**C with the calibration device removed;

FIG. **3**E is a cross-sectional view of a measurement system embodying the invention that includes a spring loaded annulus at a distal end of the measurement instrument;

FIG. **3**F is a flow chart summarizing the steps involved in calibrating a measurement instrument and taking a measurement on a material or tissue;

FIG. **4**A is a top view of a calibration device embodying the invention;

FIG. **4**B is a side view of the calibration device of FIG. **4**A.

FIG. **4**C is a plan view of the calibration device of FIG. **4**A with a calibration target removed;

FIG. **4**D is a side view of the calibration device of FIG. **4**B with a calibration target removed;

FIG. **4**E is a plan view of a calibration target with two pull tabs and a perforation down the middle designed to prevent reuse;

FIG. **5**A is a perspective view of the calibration device of FIG. **4**A;

FIGS. **5**B, and **5**C are perspective views of the calibration device of FIG. **4**A with the calibration target removed;

FIG. **6** is a schematic representation of another calibration device embodying the invention.

FIG. **7**A is a schematic side view of another calibration device embodying the invention;

FIG. **7**B is a plan view of the calibration device of FIG. **7**A;

FIGS. **8**A, **8**B, and **8**C show front, side and back views, respectively, of a measurement instrument embodying the invention;

FIG. **8**D shows a measurement instrument embodying the invention in a charging stand;

FIG. **9**A is a schematic diagram of certain elements of a measuring instrument embodying the invention;

FIG. **9**B shows a cut away view of an optical unit of the measurement instrument of FIG. **9**A;

FIG. **10** is a flowchart of a method of performing bilirubin measurements on a patient;

FIG. **11** is a diagram showing the results of data taken using the method of FIG. **10** versus a standard serum bilirubin (heel stick) method;

FIG. **12** is a diagram showing a fiber optic bundle of a measurement instrument embodying the invention adjacent a tissue or material being measured;

FIG. **13** is a sectional view of the fiber optic bundle of FIG. **12** as seen from section line **13**—**13**;

FIG. **14** is a sectional view of the fiber optic bundle of FIG. **12** as seen from section line **14**—**14**;

FIG. **15** is a diagram showing transmit and receiving fiber optics of a measurement instrument embodying the invention and the path of radiation emitted or received by the fiber optics;

FIG. **16** is a diagram showing the amplitude of radiation reflected or scattered from a patient's skin for explaining how a corrected bilirubin concentration is calculated using a method embodying the invention;

FIG. **17** is a block diagram of parts of a measurement instrument embodying the invention;

FIG. **18** is a flow chart showing the steps of a method embodying the invention for calculating bilirubin concentration of a patient;

FIG. **19** is a flow chart of another method embodying the invention for calculating a bilirubin concentration of a patient;

FIG. **20** is a diagram showing the amplitude of light reflected from a patient's skin under two conditions, the first condition corresponding to blood in the patient's skin being 100% oxygenated and the second condition corresponding to the blood in the patient's skin having no oxygen; and

FIG. **21** is a flow chart of another method embodying the invention for calculating a bilirubin concentration of a patent.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A spectrometer system that uses a disposable calibration device for calibration will be described with reference to FIGS. **1**A and **1**B.

FIG. **1A** is a schematic view of a measurement system **3** in a calibration mode. The system **3** includes an instrument **10** which outputs electromagnetic radiation **39** and receives and analyzes radiation reflected back towards the device by a material or tissue being measured. Alternatively, the instrument **10** may output, receive and analyze acoustic waves. Reference number **39** will be used to represent electromagnetic radiation or acoustic waves just as reference number **10** will be used to represent an instrument that outputs either electromagnetic radiation or acoustic waves. If the instrument **10** outputs electromagnetic radiation **39**, that radiation can lie within the visible, infrared, ultra-violet regimes, and/or within the rf, microwave and millimeter wave regimes. With regard to electromagnetic radiation **39**, the instrument **10** can be a spectrometer, laser radar, radar or any other radiation measuring instrument that outputs radiation to a material or tissue **40**, then measures some portion of the return signal. With regard to acoustic waves, the instrument **10** can be an acoustic measuring/imaging device that outputs acoustic waves and measures the return acoustic wave signal. The discussion that follows is drawn to a device that uses electromagnetic radiation, it being understood that an analogous discussion applies for an instrument that uses acoustic waves.

During a calibration procedure, as shown in FIG. **1A**, radiation **39** is transmitted toward and through a shield **20** toward a calibration target **30**. The shield **20** serves as a barrier between the instrument **10** and a material or tissue **40** to be measured, and hence functions to reduce contamination of the material or tissue **40**. One major (but not the only) purpose of the shield **20** is to guard against possible infection when living tissue **40** is measured. Hence, the shield **20** might also be referred to as an infection shield. A shield **20** must be at least partially transmissive to radiation **39** such that a portion of the emitted radiation passes through the window **20** to appear as radiation **39'**.

Radiation **39'** passes through a region **35** and reaches a surface **41** of the calibration target **30**. The surface **41** can be the same material as the calibration target **30**, or a specially applied layer. The surface **41** reflects or scatters radiation back towards the instrument **10**. Note that throughout this specification, reflection and scattering are used interchangeably and are meant to indicate that radiation travels back toward instrument **10**. Also, region **35** can include a variety of adhesives, gels, pastes, or other materials. Once system **3** with instrument **10** is calibrated, calibration target **30** is removed, and system **3** is now ready to take measurements on material **40** through shield **20**.

FIG. **1B** shows the system **3** in a measurement mode wherein calibration target **30** has been removed and radiation **39'** is now reaching a tissue or material **40** to be measured through the shield **20**.

FIG. **2A** shows a schematic representation of a calibration device **45** embodying the invention. Device **45** includes a shield supporting structure **250** with a window **260**. Together, the structure **250** and the window **260** comprise the shield **20** shown in FIG. **1A**. In an alternative embodiment, window **260** can simply be an opening in the structure **250** and the discussion regarding the window **260** should be read to encompass either an opening or a structure, where appropriate. Also, in this embodiment, the supporting structure **250** has a cone-type shape with a cut off top **265** and a window **260** that is circular shaped and is arranged to cover the top **265**. It should be understood, however, that the shape of the shield structure **250** need not be limited to a cone-type shape, and the window **260** need not be limited to a circular shape. Finally, the calibration device **45** includes a calibration target **270** (corresponding to the calibration target **30** from FIG. **1A**) with a user graspable tab **280**.

The calibration device **45** receives radiation **39** from an instrument **10**. The radiation **39** passes through the window **260** and region **35** and reaches surface **41** of the calibration target **270**. The window **260** must be at least partially (and preferably nearly completely) transparent to the radiation **39**. The region **35** can include an adhesive, gel, liquid and/or free space. In one embodiment, the window **260** is statically charged with respect to surface **41** of calibration target **270**. The static charge holds the calibration target **270** in place. Radiation **39** is then incident on the surface **41** of the calibration target **270**.

The calibration target **270** should be selected to have a known reflection spectrum for calibration purposes (note that the radiation **39** is scattered or reflected from the calibration target **270** back towards the instrument **10**). For instruments **10** which perform measurements of intensity, independent of wavelength, a highly reflective surface **41** of the calibration target **270** may be advantageous. This might include radar, laser radar and interferometric type instruments. Note, however, that such instruments might also benefit from using a less reflective surface **41** on the calibration target **270**.

Once a measurement system is calibrated, the calibration target **270** is removed (peeled) from the window **260** by pulling on a tear tab **280**, as shown in FIG. **2B**. The system **3** is now ready to take measurements on a material or tissue **40** through the window **260** of the calibration device.

FIGS. **2C** through **2E** show an embodiment of the calibration device that includes an index matching agent. As shown in these figures, the calibration device includes a structure **250**, a calibration target **270** having a calibration surface **41** and an index matching agent **293** contained within the structure **250** and covered with a seal **290**. The index matching agent **293** could be a liquid or a gel that aids the instrument in taking an accurate measurement.

To use a calibration device that includes an index matching agent, one would first remove the seal **290** using a user graspable tab **295**. The calibration device, without the seal **290**, is shown in FIG. **2D**. The calibration device would then be attached to a housing **298** of a measurement instrument, as shown in FIG. **2E**. The housing may include a window **294** designed to abut the index matching agent **293** when the structure of the calibration device is mounted on the instrument. A bundle of optical fibers **299**, that transmit and receive radiation, may abut the other side of the window **294**.

Once the structure **250** of the calibration device is mounted on the housing **298** of the measurement instrument, a calibration measurement would be performed while the calibration target **270** is still attached to the structure **250**. After the measurement instrument has been calibrated, the calibration target **270** would be removed from the structure **250** so that measurements can be performed on a material or tissue. All or a portion of the structure **250** may be made of a flexible material so that the structure **250** can flex when the instrument is pressed against the skin of a patient. This would cause the index matching agent **293** to completely fill the void between the patient's skin and the window **294** of the measurement instrument.

Another calibration device embodying the invention is shown in FIGS. **2F** and **2G**. In this embodiment, the calibration device includes a structure **250** and a window **297**. A calibration target **270** is attached to the structure **250** and an index matching agent **293** is trapped between the window **297** and the calibration target **270**.

The calibration target would be mounted on a housing **298** of a measuring instrument, as shown in FIG. **2**G. A bundle of optical fibers **299** can then abut a first side of the window **297** opposite the index matching agent **293**. Once the calibration device is attached to the measurement instrument, a calibration measurement can be performed while the calibration target **270** is still attached to the structure **250**. After calibration has occurred, the calibration target **270** could be removed so that measurements can be performed on a material or tissue.

FIGS. **3**A and **3**B correspond to FIGS. **2**A and **2**B, but with radiation **39** entering from the right hand side, and the calibration target **270** attached to the window **260** within structure **250**. In this case, an outer annular ring **306** comes into contact with a tissue or material **40** to be measured. Structure **250** also includes an annular ring or ridge **312**, which is intended to be used to secure the device **45** to an instrument **10** (not shown).

FIG. **3**C shows a measurement system **3** which utilizes a disposable calibration device **45**. Here, the measurement instrument **10** is an optical instrument, such as a spectrometer, and radiation **39** is electromagnetic radiation which can be in the visible, UV and/or infrared regions. The system **3** includes a housing **343** which is easily graspable by a human hand. The instrument **10** is coupled to calibration device **45** via optical fibers **333**. The calibration device **45** is inserted into an opening end **346** of a cone-shaped holder **358** of the housing **343**. The cone shaped holder **358** can have any shape depending, among other things, on the shape of the calibration device **45**. Hence, the holder **358** will alternatively be referred to as a calibration device receiving element. The holder **358** can be a separate piece, or part of the housing **343**. It is preferable that the holder **358** be capable of receiving the calibration device **45** and allowing the calibration target **270** to be readily removed for the calibration device so that a measurement may be performed on a material or tissue **40**. The holder **358** should also allow the calibration device **45** to be easily removed so that the system **3** is again ready to receive a new calibration device **45**.

A curved portion **366** of the housing **343** allows the user's hand to comfortably hold the system **3**. A user can initiate a calibration or measurement, as the case may be, by pressing a push button **361** with his or her thumb. Once a calibration measurement has been performed, a tear tab **280** is used to peel the calibration target **270** away from the window **260** (not shown in this view), and the system **3** is ready to make a measurement on a material or tissue **40**.

FIG. **3**D shows the same measurement system with the calibration device **45** removed. A new calibration device **45** must be inserted into the holding end **346** of the system **3**, the above discussed process of calibration repeated, and the calibration target **270** peeled away, before the measurement system **3** is ready to perform a new measurement. Alternatively, a cap **375** can be placed over the holding end **346** between measurements.

In all of the above embodiments, the calibration target **270** can have calibration information fitted directly on the surface **41** of the calibration target **270**. This calibration information can include a message read by the instrument **10** which initiates a system shut down after one or a predetermined number measurements are performed. In the case of shut down upon a single measurement, contamination is avoided because the system **3** cannot be reused on a new or different material or tissue until a new calibration device **45** replaces the used calibration device. In an alternative approach, this calibration information can be directly input into system **3** by a user, using an input interface **311**.

FIG. **3**E shows a cross-sectional view of a measurement instrument **100** embodying the invention. The instrument **100** includes a measurement device **10** coupled to an output end **370** of the system **3**. An annulus **372**, that surrounds a bundle of optical fibers **333**, is mounted on the output end **370** of the system **3**. The annulus **372** is mounted on the system **3** utilizing a spring **373**, which biases the annulus **372** outward away from the measurement system **3**. The annulus **372** may also be connected to a device that senses the position of the annulus **372** relative to the housing of the system **3**.

According to one embodiment of the invention, the measurement device functions independently of spring **373** in that a measurement can be made regardless of whether or not spring **373** is biased.

According to another embodiment of the invention, when a user performs a measurement using the measurement system **3**, the user would push the instrument **100** against the skin of a patient so that the annulus **372** moves inward, against the bias of the spring **373**. The movement would be sensed by a proximity sensing device. The proximity sensing device could then be used to output a signal when the annulus **372** is pushed far enough into the measurement system **3** such that a measurement can be performed by the measurement system **3**. In a measurement system including a spring biased annulus **373**, the proximity sensing device could be used to disable the device when the annulus **373** is too far out, and to enable the device to take a measurement when the annulus **372** is pushed a sufficient distance into the device such that a measurement can be accurately performed. The proximity sensing device could be a simple switch having electrical contacts, or a light emitter and corresponding sensor. Alternatively, the proximity sensor could directly sense the proximity of an output end of the measurement instrument **100** to the patient's skin using an optical system or some other equivalent sensor, as would be well known in the art.

FIG. **3**F summarizes the steps involved for the system **3** to take a measurement on a material or tissue **40**. In particular, step **382** involves placing a calibration device **45** on the end **346** of the system **3**. At this point, the calibration **45** device still has a calibration target **270** covering the window **260**. A calibration measurement is performed by the system **3** at step **384** by pressing a push button **361**, which activates the measurement instrument **10**. Step **388** involves removing the calibration target **270** from the window **260** using the tear tab **280**. Step **392** then involves performing a measurement on a tissue or material **40** to be measured. This might involve a single measurement or multiple measurements (if cross contamination is not an issue) on the same or a similar tissue or material. That is, if measurements are being performed on a person's skin, several measurements might be repeated in one vicinity, or at different locations on that person's body. Similarly, if measurements are being made on some type of material, multiple measurements can be made in one vicinity, or at multiple locations, provided that cross contamination is not an issue. Finally, once the measurement or measurements have been completed, the calibration device **45** is removed, discarded, and replaced with a new calibration device **45** at step **396**. Alternatively, a used calibration device **45** can be removed, discarded, and a cap **375** can be placed over the end **346** until a new measurement is to be made.

FIGS. **4**A and **4**B show a plan view and a side view, respectively, of a calibration device **45** similar, but not

identical, to the calibration device **45** shown in FIGS. **3**A and **3**B. FIGS. **4**C and **4**D show the same views as FIGS. **4**A and **4**B, respectively, with the calibration target **270** removed. The calibration device **45** can include cross-hatched lines **404**, **406**, and **408**. Lines **404**, **406**, and **408** can be placed on the backside **414** of the calibration target **270**, as well as along inner-sides **424** of the structure **250** and the outer annular ring **306** of the structure **250**, which can aid in the placement of the window **260** on a material or tissue **40** to be measured. The cross-hatched lines **404**, **406**, and **408** are designed to be aligned prior to calibration. Once the calibration measurement is made, the calibration target **270** is removed, thereby making the system **3** ready to take a calibrated measurement. If a user then tries to re-attach the calibration target **270**, they will note that the lines **404**,**406** and **408** are no longer properly aligned. Also, the surface **41** of the calibration target **270** can be made so that once a calibration measurement is made, the calibration target **270** no longer attaches or sticks to the window **260**. The cross-hatched lines **404**, **406** and **408** define six zones (here each zone is shown as a wedge, but the shape can be of any form). Also, note that an additional cross-hatched line is shown which further divides two of the wedges, and hence the number of zones need not be limited to six. Each of the cross-hatched lines are made to appear on both the calibration target **270** and the window **260**. The different zones on the calibration target **270** may have different reflectivities or different reflectance signatures. The different zones on the calibration target **270** are matched up with corresponding zones on the window **260** at the manufacturing stage. The different zones on the calibration target **270** thereby create a rotary reflectance signature. In this manner, calibration is only valid if the rotary reflectance signature is duplicated with each calibration measurement. If the calibration target **270** is not properly oriented, the calibration would not be valid. This helps to avoid the reuse of a calibration device **45** or a calibration target **270**.

The calibration target **270** can be manufactured with two pull tabs at its sides, as shown in FIG. **4**E. Here, two pull tabs **531** and **533** are attached to two halves **535** and **537** of the calibration target **270**. Between the two halves **535** and **537** is a mechanical perforation **539**. When the calibration target **270** is pulled away from the window **260** (see FIG. **2**A or **2**B) by one of the tabs, it breaks along perforation **539**, thereby making it difficult to reuse. The remaining half of the calibration target **270** can then be pulled away using the remaining tab. The perforation **539** need not be a straight line, but can be curved or spiral shaped. If the perforation **539** is a spiral, a single tab (e.g., tab **531**) can be used, in which case the calibration target **270** is unraveled and peeled away from window **260** either from its perimeter to its center (if the tab is on the perimeter of the target **270**), or from its center to its perimeter (if the tab is on the center of the target **270**). The number of revolutions of the perforation spiral can vary from less than one to three or more.

The calibration device **45** shown in FIGS. **4**B and **4**D has an annular ring **306** which contacts the material or tissue **40** to be measured. Device **45** also has a collar section **405** that attaches to an optical outlet (not shown) of the measuring instrument **10**. Diameter D1 is defined to be the diameter of the annular ring **306** and diameter D2 is defined to be the diameter of the window **260**. Height H is defined to be the distance from the window **260** to the annular ring **306**.

FIGS. **5**A, **5**B, and **5**C show three perspective views of the calibration device **45** of FIGS. **4**A–**4**D. In FIGS. **5**B and **5**C, the calibration target **270** is removed.

FIG. **6** shows a calibration device **45** according to another embodiment of the invention. Here, a landing annulus **690** is affixed to the structure **250**. The landing annulus **690** serves to fix the angle at which radiation is incident on the surface **680** of a material or tissue **40** being measured. The landing annulus **690** is preferably transparent to radiation **39**. Calibration occurs, as before, using the calibration target **270**. The calibration target **270** is then removed, and the annulus **690** remains in place. The measuring instrument, with the attached calibration device **45**, is then placed on the surface **680**, such that the annulus **690** lies flat on the surface **680**. This ensures that radiation **39** is incident approximately normal to the surface **680**, as it was to the surface **41** of the calibration target **270**. On the other hand, depending on the type of measurement, it may be preferable, due to unwanted spectral reflections, to have radiation **39** incident at an angle relative to an axis normal to the surface **680**. The landing annulus **690** can be a separate piece affixed to the structure **250** and comprised of any type of rigid material such as various plastics. If infection to the surface **680** of tissue **40** is an issue, then the landing annulus **690** should be removable from the structure **250**. Alternatively, annulus **690** can simply be an extension of window **260** itself.

The structure **250** is preferably fabricated from molded plastic with a smooth window zone defined for the window **260**. Using plastic molding allows the structure **250** to be fabricated at low cost and in a wide variety of shapes and sizes. The calibration target **270** can also be fabricated from plastic and may also have a dye or other material added to the surface **41** to provide sufficient spectral detail to effect the necessary calibration. The calibration target **270** can be attached to the window section **260** in such a way that once removed, it cannot be readily re-attached. One implementation is to fabricate the calibration target **270** using a statically clinging type plastic, and to fabricate structure **250** using an appropriate material such as an acrylic called polymethyl methacrylate (PMMA), both of which are available from 3M Corporation.

FIG. **7**A shows a side view of a calibration device **45** according to yet another embodiment of the invention. Here, the calibration target **270** is held in place by a ridge **700** alone, or together with static cling between the calibration target **270** and the window **260**. The ridge **700** can be part of the window **260**, or a separate piece. FIG. **7**B shows the calibration device **45** as viewed from above.

FIGS. **8**A, **8**B, and **8**C show front, side and back views, respectively, of a measurement system **803** embodying the invention. FIG. **8**D shows the measurement system **803** in a charging stand **871**. The elements in the measurement system **803** which have similar counterparts in the previously discussed system **3**, will also have the earlier reference numbers indicated in parenthesis.

As will be discussed with reference to FIG. **9**, the radiation analyzer **810** can include a microspectrometer such as that offered by American Laubscher Corporation of Farmingdale, N.Y. called the VIS/NIR microspectrometer. The measurement system **803** can operate in the visible, UV and/or infrared regions.

The measurement system **803** includes a housing **843** which is sized so as to be easily graspable by a human hand. A radiation analyzer **810** is coupled to the calibration device **845** via one or more optical fibers **833** (see FIG. **8**B). The calibration device **845** is inserted into an opening end **846** of a cone-shaped holder **858** of the housing **843**. A curved portion **866** of the housing **843** allows the user's hand to comfortably hold the measurement system **803**.

FIG. **8**B shows a side view of the measurement system **803**, including the radiation analyzer **810** and a push button

861. The radiation analyzer 810 is mounted on a printed circuit board (PCB) 818, which is powered by batteries 822. The batteries 822 can be recharged when the system 803 is placed in a power adapter stand through a charger connection 826. A liquid crystal display (LCD) device 832 is also coupled to the PCB 818. An LCD device 832, which is visible through a window 841, displays measurement results, instructions, warnings, and other operating information. The radiation analyzer 810 is controlled by a processor (see FIGS. 9A and 9B) also mounted on PCB 818.

FIGS. 8C and 8D show a back view of system 803, which includes back portion 891 and the LCD device 832. A person can initiate a calibration, and then a measurement, by pressing push button 861 with his or her thumb. In particular, once a calibration measurement has been performed, the tear tab 280 (see previous figures) is used to peel the calibration target 270 away from the window 260, and the system 803 is ready to make a measurement on a patient. The LCD device 832 indicates when the measurement system 803 is ready to make a calibration measurement, when a calibration measurement has been completed and the system 803 is ready to make an actual measurement, and when the system 803 has completed a measurement. The LCD device 832 also displays the results of measurements, and messages or other indicators. For instance, the LCD device 832 might show that a particular calibration target 270 has already been used and that no additional measurements can be made until a new calibration measurement is made.

A limit switch (not shown) may be installed at the end of the tip 858 to detect the presence of a calibration device 45. Once the limit switch is engaged, a calibration measurement is enabled and a measurement counter is initialized to zero. Calibration is then performed to ready the device for taking measurement. The system software then increments the counter each time a measurement is made, up to a predetermined maximum. Once the maximum number of measurements is reached, the system software indicates that a calibration is again required, and the device is prevented from taking additional measurements. Should the limit switch be disengaged at any time in the measurement sequence, indicating the removal of the disposable tip, the display indicates that a new calibration sequence must be begun before other measurements may be taken. These software controls prevent an operator from using one calibration target more than a predetermined number of times before replacing the calibration device.

FIG. 8D shows a measurement system 803 with a charging stand 871 for storing and charging the system 803. The charging stand 871 includes a center portion 873 for receiving the system 803. The center portion 873 serves as both a stand and a recharging unit. The stand 871 has an electrical cord (not shown) which can be plugged into an outlet. The stand 871 also includes an electrical receiving unit which receives charger connection 826 (see FIG. 8B) of the system 803. An indicator light 876 indicates when the measurement system 803 is properly placed in the center portion 873 so that recharging may take place. The stand 871 further includes a side receiving portion 875 which can be used to hold a supply 877 of calibration devices 845.

FIG. 9A is a schematic diagram of certain elements of a measurement system 803, and in particular, of a radiation analyzer instrument 810. The radiation analyzing instrument 810 includes an optical unit 914, a central processor unit (CPU) 905, and a memory 909. FIG. 9B shows a perspective view of an optical unit 914 that including an optical source 918, a detector array 923, an optical grating 951 and an output 955 which couples the optical unit 914 to the CPU 905 via a data bus 961. The optical source 918 may be a tungsten halogen bulb, a noble gas filled tungsten bulb or several LED's covering the desired regions of the optical spectrum. The optical source 918 may also be placed at a location in the device housing to illuminate the subject directly, without coupling the radiation into a fiber.

The embodiment shown in FIG. 9B utilizes a microspectrometer offered by American Laubscher Corporation of Farmingdale, LI, N.Y. called the VIS/NIR microspectrometer. Optical radiation 940 is output from optical source 918 and is transmitted via fiber 833 to the target (not shown) to be measured. The return signal 941 travels back down optical fiber 833 and is output from fiber end 958 into a type of waveguide 962 (cut away) and is incident on diffraction grating 951. Diffraction grating 951 achieves self-focussing of radiation 941 to different points or detectors on diode array 923, depending on the intensity and wavelengths of the return radiation 941.

The operation of system 803 will now be described in conjunction with FIGS. 9A and 9B. First, calibration target 270 starts out being arranged on window of device 45 and a user pushes a button 861, which indicates that a calibration measurement should be taken. Radiation 940 is emitted toward the calibration target 270, which reflects at least a portion of the radiation back to the measurement system. Because the calibration target 270 has a known spectral characteristic, the returned radiation 941 results in a detected intensity at individual detectors on the detector array 923, thereby yielding a measured calibration characteristic. This measured calibration characteristic is compared to the expected or known spectral characteristic of the calibration target 270, and a resulting adjustment value (which could be an array of values) is determined. Calibration target 270 is then removed, and a measurement of tissue or material 40 is made by outputting radiation 940 as above. A resulting spectral characteristic is then output from detector array 923, which in turn is adjusted by CPU 905 using the adjustment value or characteristic to yield a calibrated spectral characteristic. The calibrated spectral characteristic can then be used to determine some measurable characteristic of the material or tissue 40. One such measurement is a non-intrusive bilirubin measurement according to one embodiment of the invention, as will be discussed below.

The optical fiber 833 of measurement device 803 may comprise one or a plurality of fibers. Preferably, the optical fiber 833 comprises a plurality of fibers arranged in a bundle. FIG. 12 shows a bundle of optical fibers 333 which can be used to transmit and receive radiation. The optical fibers are arranged so that they approach a surface of a material or tissue 40 to be measured at an angle θ relative to an axis perpendicular to the surface of the material or tissue 40. When the bundle of optical fibers is inclined in this manner, backscattering effects are reduced. Angle θ is preferably not 0° and sufficiently large to prevent backscattering effects. In one embodiment, angle θ is between a few degrees and 20° and preferably between 5° and 10° and more preferably approximately 7°.

FIG. 13 shows the bundle of optical fibers 333 as seen from section line 13—13 of FIG. 12. In the bundle of optical fibers 333, there is an outer ring of transmission optical fibers 336, an inner ring of transmission fibers 337 and a central receive optical fiber 335. When the device is in operation, radiation is transmitted through the inner and outer rings of transmission fibers 336, 337, is reflected off the skin of a patient, and received by the receive optical fiber 335.

FIG. **14** shows the bundle of optical fibers as seen from section line **14**—**14** of FIG. **12**. Because the ends of the optical fibers are cut at a slight angle, and because the optical fibers themselves are cylindrical, the ends of the optical fibers appear to be ovals in FIG. **14**.

Although a microspectrometer as shown in FIG. **9**B may be used in an embodiment of the invention, other devices capable of measuring the amplitude of radiation reflected from a patient's skin at different wavelengths can also be used. For instance, FIG. **17** shows a radiation analyzing device that includes a processor **905**, a radiation source **918**, radiation conduits **833**, such as optical fibers, a memory **909** and a filter/detector unit **1000**. The filter/detector unit may comprise a plurality of detectors and filters. For instance, filters **1**, **2** and **3** **1010**, **1020** and **1030**, may be designed to pass only discreet wavelengths of the radiation reflected from a patient's skin. Each of the filters may be paired with a corresponding detector to determine the amplitude of light reflected from a patient's skin at each of the three filter wavelengths. Alternatively, the filters may be successively coupled to a single detector to determine the amplitude of the reflected light at each of the filter wavelengths. In yet another embodiment, the filter/detector unit **1000** may comprise a detector with a linear variable filter.

If the radiation conduits **833** of the device shown in FIG. **17** comprise optical fibers, the numerical aperture of the optical fibers can be selected to optimize the efficiency of the device. For instance, the optical fibers used to transmit radiation from the radiation source **918** to the patient's skin may have a numerical aperture matched to the radiation source **918**. In addition, the optical fibers used to transmit light reflected from the patient's skin to the radiation analyzer may have a numerical aperture matched to the radiation analyzer.

FIG. **15** shows a receive optical fiber **335** and four transmit optical fibers **336** and **337** surrounding the receive optical fiber **335**. The receive optical fiber **335** has a smaller numerical aperture than the transmit optical fibers **336** and **337**. The lines extending down from the bottom of the optical fibers show the path that radiation would take to leave or enter the optical fibers. For instance the area **335**A shows the path that radiation may take to enter the receive optical fiber **335**. The areas marked **336**A and **337**A show the path that radiation may take when leaving a transmit optical fiber **336** and **337**. Typically, the numerical aperture of the receive optical fiber **335** will be smaller than the numerical aperture of the transmit optical fibers **336** and **337**.

Bilirubin Measurement Process

Bilirubin can be measured in the aqueous of a patient's eye, or the sclera (white) of the eye, based on a fluorescent signature. Reflectance measurements can also be made on the tympanic membrane of the patient's ear. Finally, reflectance/scattering based measurements can be made on a patient's skin.

Current literature has indicted that the aqueous levels are likely to yield the same results as serum levels of albumin bound bilirubin. However, measurements on five jaundiced adults showed very low signal levels. Direct measurements in the aqueous are also difficult due to low signal levels. This is probably due to the photoconversion taking place in that location, i.e., too much light is allowed into the aqueous in a typical person. There are also difficulties in the evaluation due to human factors (such as the fact that infants may not stare in a particular direction for an extended period of time). Consequently, direct measurement in the aqueous is not preferred due to the low signal-to-noise ratio and poor human factors.

Direct measurements in the sclera is advantageous in that the yellow color is clearly visible, and hence the presence of bilirubin is obvious. Also, this approach is advantageous over a skin based measurement because it avoids the issue of variations in skin color or thickness. This approach was tested on five jaundiced adults. The approach yielded good signal levels, unlike the measurements in the aqueous, however, repeatability was not very good. Also, data indicated a type of photobleaching affect from the excitation light, even during the data collection interval. Spatial distribution was also not constant due, among other things, to eyelid shading. Finally, measurements on subjects shifted dramatically after those subjects spent some time outside compared to measurements taken before those subjects went outside. Consequently, direct measurement in the sclera, although yielding a high signal-to-noise ratio, is not very repeatable and encounters poor human factors.

Direct measurements on the tympanic membrane suffers from several shortcomings including poor vascularization, difficulty in determining levels of bilirubin in the membrane, and poor human factors, particularly on premature babies.

Reflectance/scattering cutaneous measurements seem to be the most promising non-invasive approach to measuring bilirubin. Also, cutaneous measurements provide a simple interface with which to work.

U.S. Pat. No. 5,353,790, the contents of which are incorporated herein by reference, presents a method and apparatus for determining bilirubin concentration in human tissue such as skin. In particular, the patent discusses reflecting light from the skin of a patient to determine a bilirubin concentration. The approach corrects for maturity-dependent optical properties of the skin, including the amount of melanin in the skin and the amount of blood in the skin. Reflected red to infrared light is used to determine the maturity-dependent optical properties, reflected red light is used to determine melanin content, and reflected yellow-orange light is used to determine the amount of blood in the skin. These quantities are used, in combination with reflected blue light, to calculate cutaneous bilirubin concentration.

U.S. Pat. No. 5,353,790 discusses the absorption spectrum of melanin and shows that the melanin absorption spectra essentially decreases linearly with wavelength in the visible region. Moreover, since the melanin absorption varies orders of magnitudes over the visible region, variations in skin pigmentation will cause large absolute changes in the absorption at the shorter wavelengths, but the same magnitude changes will cause relatively minuscule absolute changes in the very long wavelengths (>800 nm). The melanin pigmentation measured in the far red wavelength range was found to have a pivot point at around 637 nm.

A bilirubin measurement system takes advantage of the above phenomena and uses spectral reflectance to determine a serum bilirubin level in mg/dL (milligrams of bilirubin per deciliters of blood), as will now be discussed.

In the preferred methods embodying the invention for performing bilirubin measurements on a patient, patient or object readings may be compared with reference target readings to provide a meaningful output value. For example, this output value may be expressed as an optical density (OD). A formula for calculating an optical density in a method embodying the invention is shown below in Equation (1).

$$OD = \mathrm{Log}_{10} \frac{(\mathrm{Skin} - SkinDark)_s}{(Ref - RefDark)_s} \quad (1)$$

In a method embodying the invention, a measuring instrument is used with the reference target to obtain two values. First, a reading is taken against the reference target with a light source of the instrument turned off. This is referred to as a dark reference reading, which is abbreviated as RefDark in Equation (1). Next, a reading is taken on the reference target with a light source of the measuring instrument turned on. This is referred to as a reference reading, which is abbreviated Ref. in Equation (1). Both of these measurements would typically be conducted at a particular wavelength.

Next, two readings are taken on a patient's skin or on an object. The first reading is taken with the light source turned off to provide a dark skin reading. This is abbreviated SkinDark in Equation (1). Next, a reading is taken against the skin of the patient or on the object with the light source of the measuring instrument turned on to obtain a patient/object reading. This is abbreviated Skin in Equation (1). The dark skin reading is then subtracted from the skin reading to provide a corrected patient/object reading. The dark reference reading is also subtracted from the normal reference reading to provide a corrected reference reading. A negative logarithm is then taken of the ratio of the corrected patient reading to the corrected reference reading. This provides an optical density value which can be used to diagnose a condition of the patient.

FIG. **10** shows a flowchart setting forth the steps of a method embodying the invention that may be used by a measurement system to perform bilirubin measurements on a patient. The steps performed are an improved version of the approach discussed in U.S. Pat. No. 5,353,790. Step **702** involves performing a calibration measurement in a manner similar to that described above with reference to FIG. **3**E. This involves simply outputting radiation to a calibration target, and measuring the return signal (due to reflection where reflection is meant to include any type of scattering). The calibration measurement yields a measured calibration spectrum, which is compared to an expected calibration spectrum (which in turn, depends on the material of surface **41**). The difference between the expected or known spectrum and the measured spectrum serves as the calibration data. The calibration data is used to modify actual measured data, thereby compensating for unit to unit and time varying changes in source luminosity, delivery optics, collection optics, detection sensitivity, electronic drift, and environmental conditions such as temperature and humidity.

Step **704** involves making a measurement of a patient's skin by illuminating the skin with light and detecting a frequency spectrum of light reflected from the patient's skin. Step **708** involves converting the reflection (scattering) measurements into an optical density. Step **712** then involves calculating, from a first portion of the spectrum, a first parameter indicative of a maturity of the skin. Step **716** involves calculating, from a second portion of the spectrum, a second parameter indicative of an amount of melanin in the skin. Step **720** involves calculating, from a third portion of the spectrum, a third parameter indicative of a blood content of the skin. Step **724** involves calculating, from a fourth portion of the spectrum, a fourth parameter indicative of an uncorrected bilirubin concentration in the skin. Step **728** involves calculating a corrected bilirubin concentration in the skin as a function of the first, second, third and fourth parameters.

FIG. **11** shows the results of data taken using the method illustrated in FIG. **10**, versus a standard serum bilirubin (heel stick) method. The subjects were 72 full term babies of varied ethnic background, with 20 African Americans, 2 Hispanic Americans, 48 white Americans, and 2 Asian Americans. "R" represents the correlation coefficient between the measurement method described in FIG. **10**, versus the standard method of serum bilirubin. The correlation coefficient shown is 0.9165 with a perfect correlation given as 1.0000. The tests represent a purely prospective application of the method illustrated in FIG. **10**.

FIG. **18** shows a flowchart setting forth the steps of another method embodying the invention for measuring a bilirubin concentration of a patient. This second method is a more simplified method compared to the method described above.

In step **1805** the measurement system first makes a calibration measurement as described above. Next, in step **S1810**, a measurement is made using a first portion of the spectrum to determine an amplitude of the reflected light at a first wavelength. Next, in step **S1815**, a measurement is made at a second portion of the spectrum to determine an amplitude of light at a second wavelength. The first and second wavelengths are indicative of the blood content of the patient's skin. In step **1820**, a third measurement is made to determine the amplitude of the reflective light at a third wavelength indicative of an uncorrected bilirubin score. In step **S1825**, a CPU of the measurement device calculates a calibrated and corrected bilirubin concentration using the results of steps **1805** through **1820**.

The significance of making measurements at the first and second wavelengths will now be explained with reference to FIG. **20**. FIG. **20** illustrates two lines, L**3** and L**4**, that represent the amplitude of light reflected from a patient's skin under two different conditions. In a first condition, the blood flowing through the patient's skin is fully oxygenated. In the second condition, the blood flowing through the patient's skin has no oxygen attached to the hemoglobin in the blood. As shown in FIG. **20**, lines L**3** and L**4** cross one another at two points H and I. Experimental results have indicated that the wavelengths corresponding to points H and I are at approximately 526 and 585 nanometers, respectively.

By making the measurements of the amplitude of light reflected from a patient's skin at approximately 526 nanometers and 586 nanometers, it is possible to obtain a measurement representative of the blood content of the patient's skin. Because the measurements are made at the crossover points, it does not matter whether the blood in the patient's skin is fully or partially oxygenated.

The method of calculating a calibrated and corrected bilirubin concentration of FIG. **18** will now be further explained with reference to FIG. **16**. In FIG. **16**, L**5** represents an amplitude of light reflected from a patient's skin at various wavelengths.

The amplitude of light reflected from a patient's skin at a first wavelength, as measured in step **1810**, is taken at a wavelength of approximately 526 nanometers. The amplitude at this wavelength is represented by point B in FIG. **16**. The amplitude of the light reflected from the patient's skin at the second wavelength is taken at approximately 586 nanometers, which is represented by point C in FIG. **16**. An imaginary line L**1** is drawn through points B and C and backwards through smaller wavelengths of the visible light spectrum. The amplitude value at the intersection of the line L**1** and an imaginary line at 476 nanometers is then

determined, which is represented by point D in FIG. **16**. Point A in FIG. **16** represents the measured amplitude of the light reflected from the patient's skin at 476 nanometers. The value of point D is then subtracted from the value of point A to determine a corrected bilirubin score. This corrected bilirubin score is then used with the calibration data taken during a calibration measurement to determine a calibrated and corrected bilirubin concentration of the patient's skin.

The second method described above is far more simple than the first method, as it only involves taking amplitude measurements of reflected light at three discreet wavelengths. Experimental results have shown that the second method provides substantially the same level of accuracy as the first method, and in some cases the second method produces even better results.

An additional method of determining a bilirubin concentration in a patient's skin will now be described with reference to FIG. **19**. FIG. **19** shows a flowchart of the steps of a third method of determining a patient's bilirubin concentration. In step **1905**, a calibration measurement is taken as described above. In step **1910**, measurements of the amplitude of light reflected from a patient's skin are made at first, second, third, fourth and fifth wavelengths. In step **1915**, the first, second and third measurements are adjusted based on the fourth and fifth measurements. In step **1920**, a calibrated and corrected bilirubin concentration is calculated using the calibration measurement and the adjusted first, second and third measurements.

The first, second and third measurements taken during step **S1910** are taken at the wavelengths 476 nanometers, 526 nanometers, and 586 nanometers as described above in connection with the second method. The fourth and fifth measurements are taken at wavelengths J and K, as shown in FIG. **16**, which are represented by the points M and N. The wavelengths corresponding to J and K are in the range between 600 and 700 nanometers. The amplitude of the light reflected from the patient's skin at frequencies J and K are representative of melanin in the patient's skin. A line drawn through the amplitude points M and N corresponding to J and K will have a negative slope that indicates the amount of melanin in the patient's skin. The greater the negative slope (or the more steeply the line is inclined down toward the right) the greater the amount of melanin.

In step **1915**, the first, second and third measurements are adjusted based on the fourth and fifth measurements. To accomplish this adjustment, a line L**2** is drawn through points M and N, and the line L**2** is projected backwards through the smaller wavelengths, as shown in FIG. **16**. Points of intersection of the line L**2** with imaginary lines at the first, second and third wavelengths are determined. These points are shown as points E, F and G in FIG. **16**. The amplitude values of points E, F and G are then subtracted from the respective measurements made at these wavelengths, which are shown as points C, B and A. These adjusted measurements for the first, second and third wavelengths are then used to determine a calibrated and corrected bilirubin concentration for the patient according to the methods described above.

FIG. **21** shows a flowchart setting forth the steps of another method embodying the invention that may be used by a measurement system to perform bilirubin measurements on a patient. Step **2105** involves performing a calibration measurement in a manner similar to that described above with reference to FIG. **3**E. This preferably involves outputting a radiation to a calibration target, and measuring the return signal (due to reflection where reflection is meant to include any type of scattering). The calibration measurement yields a measured calibration spectrum, which is compared to an expected calibration spectrum (which in turn, depends on the material of surface **41**). The difference between the expected or known spectrum and the measured spectrum serves as the calibration data. The calibration data is used to modify actual measured data, thereby compensating for unit to unit and time varying changes in source luminosity, delivery optics, collection optics, detection sensitivity, electronic drift and environmental conditions, such as, for example, temperature and humidity.

Step **2110** involves making a measurement of a patient's skin with light and detecting a frequency spectrum of light reflected from the patient's skin at first, second and third portions of the spectrum. Preferably, the first portion of the spectrum is representative of blood content in the skin, for example, measurements may be taken at wavelengths of ~563–566 nm. The measurement of the second portion of the spectrum preferably gives melanin and scattering values, for example, measurements may be taken at wavelengths of ~517–518 nm. The measurement at the third portion of the spectrum gives an uncorrected bilirubin concentration in the skin, for example, measurements may be taken at wavelengths of ~484 nm.

Step **2115** involves adjusting the measurement made at the third portion of the spectrum using the measurements made at the first and second portions of the spectrum. Step **2120** involves calculating a calibrated and corrected bilirubin concentration using the calibration measurement and the adjusted third measurement.

Both the skin and reference readings described above may be corrected for "stray light." The passband of the waveguide used in this embodiment transmits light from 380 nm to 780 nm. Therefore, any signal (light) that is outside of this waveband is considered "stray light" because it is scattered signal and not real, information carrying signal. One preferred method for correcting for stray light is described below with reference to Equation (2).

$$(I(\lambda))_s = \left(I(\lambda) - \left[I(330) - \frac{I(330) - I(900)}{(900 - 300)} * (\lambda - 330)\right]\right) \quad (2)$$

If I(λ) represents a measured intensity at a particular wavelength, the intensity valve can be corrected for stray light using Equation (2) shown above. The correction for stray light requires that the intensity of light be measured at 330 nm to provide a value I(330), and that the intensity of light at 900 nm be measured to provide a value I(900). These values are then inserted into Equation (2), shown above, to provide a stray light corrected intensity value $(I(\lambda))_S$. These stray light corrected intensity values can then be used in Equation (1) above to provide an optical density value which can be used to diagnose a condition of a patient.

Another method of calculating a corrected bilirubin concentration utilizes a simple equation where the optical densities at three wavelengths are multiplied by coefficients, and the products are then added. For instance, a bilirubin concentration (Bili) could be calculated using equation (3) set forth below.

$$\text{Bili} = \alpha_1 OD_{\lambda 1} + \alpha_2 OD_{\lambda 2} + \alpha_3 OD_{\lambda 3} \quad (3)$$

In equation (3), OD_λ is the optical density, or amount of light at a particular wavelength λ and α_1, α_2 and α_3 are experimentally determined coefficient values. Preferably, the "stray light" correction method discussed above is used

to calculate intensities, which in turn are used to calculate optical density values which are utilized in Equation (3) to calculate the bilirubin concentration (bili).

However, in other methods, a "stray light rejection (SLR)" value could be added to the equation, as set forth in equation (4) below.

$$Bili=\alpha_1 OD_{\lambda 1}+\alpha_2 OD_{\lambda 2}+\alpha_3 OD_{\lambda 3}+\beta * SLR \quad (4)$$

In equation (4), SLR is an experimentally determined value which represents the characteristics of an individual device, and β is an experimentally determined coefficient. The SLR value would be determined by testing a device after it is assembled. The value could be a predetermined coefficient.

In Equation (4), the intensity values used to calculate the optical density values $OD_{\lambda 1}$, $OD_{\lambda 2}$, and $OD_{\lambda 3}$ would not be corrected for stray light using Equation (2). Instead, the optical density would be calculated using the actual measured intensity values at the particular wavelengths.

In a preferred embodiment, after a measuring device is assembled, the device would be used to take one or more readings on a reference or calibration standard. The readings would attempt to determine whether the device appears to detect any light at wavelengths outside or at the edges of the devices's operating range. The results of these measurements would then be used to calculate a stray light rejection factor SLR.

The SLR could then be input into a device's long term memory. This could allow the device to calculate a bilirubin concentration using an equation like Equation (4), which makes use of the experimentally determined SLR.

Many alternatives and modifications of the above examples would be apparent to those skilled in the art upon reading the foregoing or practicing the invention. The apparatus and methods described above are intended to be exemplary and are not intended to limit the scope of the invention as defined by the following claims.

What is claimed is:

1. A method for determining a bilirubin concentration of a patient, comprising the steps of:

a) illuminating a portion of a skin of the patient with light;

b) detecting a frequency spectrum of light scattered from the skin;

c) determining, from first and second portions of the spectrum, a first parameter indicative of a blood content of the skin and a second parameter indicative of a melanin content of the skin;

d) determining, from a third portion of the spectrum, a third parameter indicative of an uncorrected bilirubin concentration; and

e) calculating a corrected bilirubin concentration based on at least one calibration factor corresponding to at least one of the first, second, and third parameters and values consisting essentially of the first, second and third parameters.

2. The method of claim **1**, further comprising the step of performing a calibration measurement on a calibration target and storing resulting calibration data prior to illuminating the patient's skin with light, wherein the at least one calibration factor included in the step of calculating a corrected bilirubin concentration is based on the calibration data.

3. The method of claim **1**, wherein the first and second portions of the spectrum are at centered at wavelengths of approximately 563–566 nm and approximately 517–518 nm, respectively.

4. The method of claim **3**, wherein the third portion of the spectrum is centered at a wavelength of approximately 484 nm.

5. The method of claim **1**, wherein the third portion of the spectrum is centered at a wavelength of approximately 484 nm.

6. The method of claim **1**, wherein the performance of steps a–e result in a first corrected bilirubin concentration, further comprising the steps of:

f) repeating steps a–e to calculate a second corrected bilirubin concentration; and

g) calculating an average corrected bilirubin concentration based on the first and second corrected bilirubin concentrations.

7. The method of claim **6**, wherein different portions of the patient's skin are illuminated each time steps a–e are performed.

8. The method of claim **7**, wherein the different portions of the patient's skin are located on different portions of the patient's body.

9. The method of claim **1**, wherein the performance of steps a–e result in a first corrected bilirubin concentration, further comprising the steps of:

f) repeating steps a–e at least twice to calculate at least second and third corrected bilirubin concentrations;

g) calculating an average corrected bilirubin concentration and a standard deviation using at least the first, second and third corrected bilirubin concentrations;

h) comparing the calculated standard deviation to a predetermined maximum standard deviation; and

i) repeating steps a–g if the calculated standard deviation exceeds the predetermined maximum standard deviation.

10. A system for determining a bilirubin concentration in a patient, comprising:

means for illuminating a portion of the patient's skin with light;

means for detecting a frequency spectrum of light scattered from the skin;

means for determining, from first and second portions of the spectrum, a first parameter indicative of a blood content of the skin and a second parameter indicative of a melanin content of the skin;

means for determining, from a third portion of the spectrum, a third parameter indicative of an uncorrected bilirubin concentration; and

means for calculating a corrected bilirubin concentration based on at least one calibration factor corresponding to at least one of the first, second, and third parameters and values consisting essentially of the first, second and third parameters.

11. The system of claim **10**, further comprising:

means for performing a calibration measurement on a calibration target and for storing resulting calibration data, wherein the at least one corresponding calibration factor used by the means for calculating a corrected bilirubin concentration is based on the calibration data.

12. The system of claim **10**, further comprising:

means for calculating an average corrected bilirubin concentration and a standard deviation using at least three calculated corrected bilirubin concentrations; and

means for comparing the calculated standard deviation to a predetermined maximum standard deviation.

13. The system of claim **10**, further comprising means for holding a removable calibration target that can be used to

calibrate the system prior to determining the bilirubin concentration of a mammal.

14. The system of claim **13**, further comprising a removable calibration target mounted on the calibration target holding means.

15. The system of claim **14**, wherein the removable calibration target comprises a structure that remains attached to the calibration target holding means after a portion of the removable calibration target is removed to allow a measurement to be made.

16. A system for measuring a bilirubin concentration of a patient by directing radiation onto a portion of a skin of the patient and analyzing scattered or reflected radiation returning from the skin, comprising:

a radiation analyzing device for analyzing radiation scattered or reflected from the patient's skin and for outputting radiation data;

a radiation source;

at least one radiation transmitting conduit for directing radiation from the radiation source to a portion of the patient's skin;

at least one radiation receiving conduit for directing radiation scattered from the patient's skin to the radiation analyzing device; and

means for calculating a bilirubin concentration of the patient based on calibrated measurements of the reflected or scattered radiation at first and second wavelength bands indicative of a blood content of the patient's skin, and of a melanin content of the patient's skin, respectively, and on a calibrated measurement of the reflected or scattered radiation at a third wavelength band indicative of the patient's bilirubin concentration.

17. The system of claim **16**, wherein the at least one radiation transmitting conduit directs radiation at the patient's skin at acute angle relative to an axis perpendicular to the skin surface.

18. The system of claim **17**, wherein the angle is approximately twelve degrees.

19. The system of claim **17**, wherein the angle is large enough to reduce radiation backscattering.

20. The system of claim **16**, wherein the at least one radiation transmitting conduit comprises a plurality of radiation transmitting conduits, and wherein the at least one radiation receiving conduit is surrounded by the plurality of radiation transmitting conduits.

21. The system of claim **20**, wherein the plurality of radiation transmitting conduits are arranged in first and second annular rings, the first annular ring surrounding the at least one radiation receiving conduit, and the second annular ring surrounding the at least one radiation receiving conduit and the first annular ring.

22. The system of claim **16**, wherein a numerical aperture of the at least one radiation transmitting conduit is matched to the radiation source, and wherein a numerical aperture of the at least one radiation receiving conduit is matched to the radiation analyzing device.

23. The system of claim **22**, wherein the numerical aperture of the at least one radiation transmitting conduit is different from the numerical aperture of the at least one radiation receiving conduit.

24. The system of claim **16**, further comprising a window located between the radiation transmitting and receiving conduits and an exterior measuring end of the system, wherein the window comprises a soft polymer that acts as an index matching agent between the radiation transmitting and receiving conduits and the patient's skin.

25. The system of claim **16**, wherein a length of the at least one radiation receiving conduit is sufficiently long such that mode scrambling occurs.

26. The system of claim **16**, further comprising a proximity sensing device for sensing a proximity of a distal end of the radiation transmitting and receiving conduits to the patient's skin.

27. The system of claim **26**, wherein the system only measures the condition of the patient when the proximity sensing device indicates that the radiation transmitting and receiving conduits are within a predetermined proximity to the patient's skin.

28. The system of claim **26**, wherein the proximity sensing device comprises a spring loaded annulus that surrounds the radiation transmitting and receiving conduits.

29. The system of claim **16**, further comprising a transmitter for transmitting data regarding the calculated condition of the patient to a remote recording device.

30. The system of claim **29**, wherein the transmitter comprises an infrared transmitter.

31. The system of claim **16**, wherein the radiation analyzing device comprises a spectrometer.

32. The system of claim **16**, wherein the radiation analyzing device comprises a diffraction grating and a plurality of detectors, wherein the diffraction grating focuses radiation having predetermined wavelengths on respective ones of the plurality of detectors.

33. The system of claim **16**, wherein the radiation analyzing device comprises at least one radiation detector and a plurality of radiation filters, each of the plurality of radiation filters allowing only a narrow wavelength band of radiation to reach the at least one radiation detector.

34. The system of claim **16**, wherein the radiation analyzing device comprises a radiation detector and a linear variable filter for allowing selected wavelengths of radiation to reach the radiation detector.

35. A method for determining a bilirubin concentration of a patient, comprising the steps of:

a) illuminating a portion of a skin of the patient with light;

b) detecting a frequency spectrum of light scattered from the skin;

c) determining, from first and second portions of the spectrum, a first parameter indicative of a blood content of the skin and a second parameter indicative of a melanin content of the skin;

d) determining, from a third portion of the spectrum, a third parameter indicative of an uncorrected bilirubin concentration; and

e) correcting the first, second and third parameters based on a calibration factor, and calculating a corrected bilirubin concentration based on the corrected first, second and third parameters.

36. The method of claim **35**, further comprising the step of performing a calibration measurement on a calibration target and storing resulting calibration data prior to illuminating the patient's skin with light, wherein the calibration factor used to correct the first, second and third parameters is based on the calibration data.

37. The method of claim **35**, wherein the first and second portions of the spectrum are at centered at wavelengths of approximately 563–566 nm and approximately 517–518 nm, respectively.

38. The method of claim **37**, wherein the third portion of the spectrum is centered at a wavelength of approximately 484 nm.

39. The method of claim **35**, wherein the performance of steps a–e result in a first corrected bilirubin concentration, further comprising the steps of:

f) repeating steps a–e to calculate a second corrected bilirubin concentration; and

g) calculating an average corrected bilirubin concentration based on the first and second corrected bilirubin concentrations.

40. The method of claim **35**, wherein the performance of steps a–e result in a first corrected bilirubin concentration, further comprising the steps of:

f) repeating steps a–e at least twice to calculate at least second and third corrected bilirubin concentrations;

g) calculating an average corrected bilirubin concentration and a standard deviation using at least the first, second and third corrected bilirubin concentrations;

h) comparing the calculated standard deviation to a predetermined maximum standard deviation; and

i) repeating steps a–g if the calculated standard deviation exceeds the predetermined maximum standard deviation.

41. A system for determining a bilirubin concentration in a patient, comprising:

means for illuminating a portion of the patient's skin with light;

means for detecting a frequency spectrum of light scattered from the skin;

means for determining, from first and second portions of the spectrum, a first parameter indicative of a blood content of the skin and a second parameter indicative of a melanin content of the skin;

means for determining, from a third portion of the spectrum, a third parameter indicative of an uncorrected bilirubin concentration; and

means for calculating a corrected bilirubin concentration based on corrected parameters corresponding to the first, second and third parameters.

42. The system of claim **41**, further comprising:

means for performing a calibration measurement on a calibration target and for storing resulting calibration data, wherein the corrected parameters are based on the calibration data.

43. The system of claim **41**, further comprising:

means for calculating an average corrected bilirubin concentration and a standard deviation using at least three calculated corrected bilirubin concentrations; and

means for comparing the calculated standard deviation to a predetermined maximum standard deviation.

44. The system of claim **41**, further comprising means for holding a removable calibration target that can be used to calibrate the system prior to determining the bilirubin concentration of a mammal.

45. The system of claim **44**, wherein a removable calibration target mounted on the calibration target holding means comprises a structure that remains attached to the calibration target holding means after at least a portion of the removable calibration target is removed to allow a measurement to be made.

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