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<p>(21) International Application Number: PCT/DK91/00152</p> <p>(22) International Filing Date: 6 June 1991 (06.06.91)</p> <p>(30) Priority data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">PK 0489</td> <td style="width: 40%;">6 June 1990 (06.06.90)</td> <td style="width: 30%;">AU</td> </tr> <tr> <td>PK 4310</td> <td>22 January 1991 (22.01.91)</td> <td>AU</td> </tr> </table> <p>(71)(72) Applicant and Inventor: CLIFT, Vaughan [AU/DK]; Ordrupvej 102, DK-2920 Charlottenlund (DK).</p> <p>(74) Agent: NOVO NORDISK A/S; Patent Department, Novo Allé, DK-2880 Bagsvaerd (DK).</p> <p>(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.</p>		PK 0489	6 June 1990 (06.06.90)	AU	PK 4310	22 January 1991 (22.01.91)	AU	<p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: METHOD AND DEVICE FOR IN VIVO MEASURING BLOOD SUGAR LEVELS</p>								
<p>(57) Abstract</p> <p>The concentration of a substance, especially glucose, in the blood is measured in vivo by applying to the skin two wavelengths of infrared light and measuring the difference in the absorption of the two wavelengths, preferably in the range of 3-10 μm, one being a sample wavelength at which the substance shows a specific absorption and the other being a reference wavelength at which the substance shows no specific absorption. Simultaneously the concentrations of interfering components are measured in the same way and the result for the substance is corrected with regard to the measured concentrations of interfering components. Infrared light is transmitted through optical fibres (10, 10a) to a detector having two chambers (15, 15a), a sample wavelength to one chamber (15) and a reference wavelength to the other (15a), and a transducer (14) between the chambers measures the difference in the pressures induced in the respective chambers when the tissue beneath the chambers is heated by absorption of the infrared light transmitted to it.</p>								

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METHOD AND DEVICE FOR IN VIVO MEASURING BLOOD SUGAR LEVELS

The present invention concerns a method and a device for measuring in vivo blood sugar levels.

Continuous maintenance of normal blood sugar levels is important in avoiding the deterioration of a number of body organs. For example it is considered a prerequisite in prevention of the progression of diabetic microangiopathy in the kidney, the retina, and in autonomic and peripheral nerves. However, under normal conditions for managing a diabetic condition it is virtually impossible to maintain blood sugar concentrations continuously at normal levels. This is largely because the uptake of carbohydrates and conversion to glucose in the blood is not predictable. Blood sugar levels are normally determined by regular in vitro measurements and the quantity of insulin required to maintain normal blood sugar levels is based on predictions of glucose uptake and consumption during the period between measurements. Thus for example if diabetics find themselves in the position of engaging in unpredicted exercise especially after an injection of insulin, they can all too readily become comatose. Diabetes is hence very difficult to manage in children and adults. Also in the unwell or premature neonate reserves of glucose are limited and control mechanisms immature predisposing them to dangerously low blood sugar levels.

At present blood sugar levels are normally determined by regular in vitro measurements requiring puncturing the skin, taking away a blood sample and using an in vitro method which usually takes two minutes. This induces considerable restraint on taking blood sugar measurements. These constraints on measuring blood sugar levels and poor predictability of blood glucose levels have significant impact on the lifestyle of a diabetic patient and the well being of any seriously ill patient.

As a result of these difficulties in managing a diabetic condition there is a long standing need for a device that is capable of continuously measuring in vivo blood sugar levels. Such a device could be used for controlling the injection of insulin into the blood in response to increases in blood sugar levels. Such a device is known

as an artificial pancreas. Attempts have been made to combine in vivo determination of blood sugar levels with an insulin pump controlled by a micro-computer. However, these have been a failure because the method of continuously monitoring blood sugar levels was not reliable. Attempts have been made to make continuous blood
5 sugar measurement in vivo using presently available enzyme techniques such as glucose oxidase reduced onto an electrode. These devices comprise in general the coating of an anode with an enzyme specific for glucose, covering this with a glucose permeable membrane and measuring a small potential difference, or current, between this electrode inserted into a subcutaneous layer with another
10 electrode. However, the method has proved unreliable because the currents and/or potentials are minute and subject to electrical noise, the membranes become coated by the body preventing the diffusion of glucose into the electrode and small molecules like uric acid, enzymes and other factors destroy the enzyme.

Optical methods have also been previously suggested for measuring the
15 glucose molecule using its physical properties such as refractive index, ability to rotate the plane of polarised light and absorption in the infra-red spectrum, especially the near infra-red. For instance, in published Canadian Patent No. 1,247,397 there is disclosed an I.R. absorption method using discrete frequencies of near infra-red light and light transmitted or diffusely reflected from the irradiated tissue. The
20 difficulty with such a method is discussed below.

Infrared spectroscopy has been proposed as an alternative to electrochemical techniques for continuously monitoring in vivo blood sugar levels. The problems associated with such a proposal are described in an article published in the International Journal of Artificial Organs, Vol. 12, No. 2 1988, pages 129 to 135 "Artificial
25 Pancreas Blood Glucose Measured by Infrared Spectroscopy" by H. Zeller, P. Novak and R. Landgraf. The principal difficulty concerns the strong background absorption spectra of water and other blood constituents which make distinguishing the "fingerprint" of glucose difficult. This absorption is so strong as to effectively prevent any method using mid to far I.R. light transmitting the light through any volume of
30 tissue.

Another difficulty in near I.R. is that the technique requires the maintenance of a fixed path length of sample through which the light passes. Also, the varying concentrations of the other components of blood which also absorb I.R. light produce significant error in measurement.

5 Until now research had concentrated on infra-red spectroscopy or photometric methods in the near infra-red as wavelengths of light in this region are capable of penetrating through flesh. However, wavelengths beyond this range have the advantage that absorption by the glucose molecule is stronger and more sharply delineated permitting it to be more readily differentiated from the other components
10 of blood.

Attempts to use the near infra-red have largely been unsuccessful because of the limited absorption by the markedly attenuated glucose overtones in this region and the overlying spectra of numerous molecules including water. Also the systems previously described have had to maintain a fixed path length.

15 Other methods such as are disclosed in Swiss patent CH 612,271 have described the use of A.T.R. (Attenuated Total Reflection) prisms and the use of spectroscopy by means of a Fourier Transform Infra-red Spectroscope. These methods have been made inaccurate by the inability of such a method to accurately correct for the varied concentrations of other components of blood, for example,
20 varying haemoglobin and fat, whose spectra overlay that of glucose (see also Clinical Chemistry Vol 35, No. 9 1854-1856). The light must enter and exit the prism at a precise angle and a fluid being examined must cover a constant surface area. These requirements as well as other variables such as temperature of the prism, make the application to a patient difficult and remote sensing, such as bed side
25 monitoring, impossible. Also the "evanescent" wave produced by these A.T.R. systems penetrates less than 1 micron into the surrounding fluid making them impossible to use across a membrane or through skin for measuring blood sugar.

Methods have also been described which use such sources as CO₂ lasers as a source of discrete frequencies absorbed by the glucose molecule. These methods
30 too cannot compensate for the varying concentrations of protein and fat and their effect on accuracy. They have the added disadvantage of requiring expensive and

highly specialized bulky equipment and present some risk of burning the tissue being assayed.

It is, therefore, the object of the invention to provide a method for in vivo measurement of the concentration of glucose in the blood by which method these 5 difficulties are overcome and the measurement may be made using an inexpensive and portable system despite the varying concentrations of interfering substances such as other blood constituents including protein and fat.

This is obtained by a method in which the absorption of selected wavelengths of infrared light is measured the method being characterized in that light of the 10 selected wavelengths is selected from the range 1 - 40 μ m and is transmitted to the tissue of a person whose blood is being tested for its content of the substance, that at least one of the wavelengths is selected from the range 3 - 10 μ m, that the concentration is measured for the substance as well as for interfering components using for each substance or component to be measured two different wavelengths 15 of infrared light, one being a measuring wavelength at which the component or substance shows a specific absorption and the other being a reference wavelength at which the component or substance shows a low absorption, that a detector placed in or on the skin is used, and that the result of the measuring of the substance is corrected by taking into account the absorption caused by the interfering com- 20 ponents at the measuring and the reference wavelengths for the substance.

Known methods have concentrated on infrared spectroscopy in the near range from 0.700 to 1.5 μ m as these wavelengths are capable of penetrating skin. Infrared spectroscopy in the far infrared range has been ignored as it has difficulty penetrating the skin and the weak measurement signals are heavily disturbed by 25 absorption in the other blood constituents, water, protein and fat. However, the glucose molecule is more readily differentiated from the other components of the blood by its absorption spectrum in the far infrared range especially in the range 9-10 μ m.

By the method according to the invention, profit is taken from the clearer 30 "finger prints" of glucose in the far infrared range and the "noise" caused by the absorption in other blood components is compensated for by simultaneously

measuring the concentrations of these components with separate reference sample wavelengths and compensating for the error in measurement these produce using experimentally derived constants.

A similar system has been used successfully in a commercial device called
5 a Foos Milko-scan 104 A/B for the measurement of lactose in samples of dairy products (see US patent 931621). This system analyses milk using transmission through a sample in a test cuvette and measures the light absorbed using a thermopile light detector. Such a system is of course not applicable to in vivo measurement of glucose but serves to illustrate the efficacy of the principle.

10 The light may be transmitted to the tissue beneath the outer layer of skin and the absorption be measured by attenuated total reflection. By this invasive method and measurement the difficulty of the longwave infrared light, not penetrating the skin, is overcome, but the light may also non-invasively be transmitted to the outer side of the skin and the absorption may be measured by detecting the heat
15 generated in the tissue, both these methods may be applied non-invasively to areas where the tissue is not covered by thick layers of epithelium such as inside the mouth.

The light transmitted to the tissue may be modulated and using different modulation frequencies for the different wavelengths of light used for measuring the
20 concentration of different components the different pairs of wavelengths may be discriminated.

If, further, the different modulation frequencies are not harmonic the respective pairs of measuring and reference wavelengths may be discriminated even if they are transmitted simultaneously through the same transmission channel.

25 If the modulation of the measuring wavelength and the modulation of the reference wavelength is not in phase these measurements performed by each of these wavelengths may also be discriminated. By this method problems such as changing temperature or exposed surface areas may be overcome as both wavelengths, sample and reference, are exposed to the same conditions.

30 The modulation may be provided by chopping the light.

The results of the measurements may appear as computable electric signals, and the correction and interpretation of the measured values may be made by calculation performed on the electric signals.

The substance, the concentration of which is measured, is preferably glucose, 5 but the method may also be used for measuring the concentration of CO₂ or ethanol in the blood, or the product of enzymic reaction of glucose.

The sample wavelength and the reference wavelength used are preferably for glucose 9.5 ±0.5 μm and 7.7 ±0.5 μm, respectively, or 3.47 ±0.5 μm and 2.96 ±0.5 μm, respectively, for fat 5.74 ±0.5 μm and 5.58 ±0.5 μm, respectively, or 3.513 ±0.5 10 μm and 3.57 ±0.5 μm, respectively, for protein 6.5 ±0.5 μm and 6.7 ±0.5 μm, respectively.

The invention also comprises an apparatus for carrying out the method. According to the invention such an apparatus comprises a light aggregate able to provide selectable narrow light bands in the wavelength range of 1 -40 μm whereof 15 at least one band lies in the range of 3 - 10 μm, means for transmitting light from the aggregate to the tissue of a person whose blood is being measured for its content of the substance, a detector designed to be placed in or on the skin and detecting the absorption of light in the the tissue by providing electric signals representative of the light absorption detected, and a computer calculating the concentration of the 20 substance on the basis of the detected light absorption values.

The light aggregate may comprise a wide-banded light source and a number of filters each transmitting one of the selected narrow bands, or it may comprise a number of surface emitting light emitting diodes each emitting infrared light of a chosen wavelength.

25 The light aggregate may further comprise means for focusing the light on an optical coupling means for the light transmitting means.

Further the light aggregate may comprise chopper means for chopping at preset chopping frequencies the light wave bands transmitted from the light aggregate. The chopper means may be mechanical in the shape of a rotating 30 diaphragm with cut-outs, or when the light aggregate comprises a number of light

emitting diodes or semi-conductor thermal source, an electronic circuit controlling the energization of the light diodes or semi-conductor thermal sources.

The detector may in its invasive form comprise an optical device which in its simplest form consists of an input optical fibre transmitting light from the light
5 aggregate, a gap filled with tissue fluid or blood across which light passes and the light transmitted passing through an output fibre to a light detector.

The detector may in its invasive form comprise an optical needle probe ATR all having an input fibre and an output fibre and at the output fibre a light detector providing an output signal representing by an electrical signal the light absorption
10 measured. The sensitivity of such an ATR cell may be enhanced by the addition of a thin metal coating to the outside of the cell such that it acts as a surface plasma resonance device.

The detector may have an overlying jacket of a glucose permeable membrane with a gap for fluid to collect to decrease the concentration of interfering substances
15 further. The detector may also in its invasive form use the glucose permeable membrane jacketed ATR needle in conjunction with an enzyme and the method be used to measure glucose indirectly by means of measuring a product of enzymic reaction the infra-red absorption of which is measured in the same way as for glucose.

20 For non-invasive measurement the detector may comprise a pair of chambers having an open side placed against the skin on the measuring spot, and a pressure transducer measuring the pressure difference between the chambers and representing this differential pressure by an electric signal. The one chamber has at its side opposite the open side an inlet for infrared light radiation transmitted from
25 the light aggregate. This construction makes it possible to detect the pressure produced in the chamber lying over the tissue which receives infrared light radiation when the absorption of this radiation is converted into heat in the tissue. Commonly made noises, e.g. those due to the pulse movement or due to pressure changes caused by common temperature variations in the skin, will automatically be rejected.

30 Such a method for use with ultra violet and visible light has been used for measurement of skin pigment and was published by Drs Poulet and Chambron in

The Journal of Medical and Biological Engineering and Computing, 1985, 23, 585-588. A similar method is described in European patent application No. 282,234. However, in the method we are using, light from the mid to far infra-red region is used which has not been described previously for an in vivo application. Also, in
5 such previously described methods there is no method to solve the problem of interfering substances producing error in a quantitative assay, a problem overcome by this method.

Using such a two chamber detector receiving infrared light radiation in both its chambers makes it possible to measure the response produced by the light
10 absorption of a sample wavelength against the response produced by the corresponding reference wavelength.

To compensate for noise caused by vibrations in the direction perpendicular to the diaphragm of the pressure transducer between the chambers a further transducer may be added to each chamber at the ends thereof and with their
15 diaphragms in planes parallel with the diaphragm of the transducer between the chambers.

Another important source of disturbance is sweat secreted into the chambers. This may be eliminated by letting each chamber having an inlet for infrared radiation, communicate with a compartment containing a desiccant. In this way the water may
20 be removed whereas the pressure provided in the chamber is maintained. This may also be achieved by means of a rigid but water permeable membrane to transport the water to the outside.

In the following, the invention will be explained with reference to the drawings, wherein

- 25 Fig. 1 schematically shows a light aggregate for providing chopped infrared radiation of chosen wavelengths,
 Fig. 2 shows a diaphragm used for providing different chopping frequencies,
 Fig. 3 schematically shows a side elevation view of an optical fibre
30 detector with ATR needle probe,

- Fig. 4 shows details of an ATR needle probe with an internal infusion canal,
- Fig. 5 shows details of an ATR needle probe attached to an infusion needle,
- 5 Fig. 6 shows an optical fibre detector with an ATR needle probe with separate input fibres for each wavelength,
- Fig. 7 schematically shows an ATR needle probe inserted through the skin,
- Fig. 8 shows a detector detecting the heat response of the tissue
10 beneath the skin when infrared radiation is transmitted to the skin,
- Fig. 9 shows another embodiment of a heat response detector,
- Fig. 10 shows a further development of the heat response detector in Fig. 9,
- 15 Fig. 11 shows an electric coupling adding the outputs from the transducers of the detector in Fig. 10,
- Fig. 12 shows a heat response detector with an infrared radiation source in the form of emitting diodes carried on the detector,
- Fig. 13 shows seen from the bottom a double detector of the kind
20 shown in Fig. 9,
- Fig. 14 schematically shows a view from the bottom of a triplicated detector of the kind shown in Fig. 9.
- Fig. 15 shows another embodiment of the detector with a desiccant chamber,
- 25 Fig. 16 shows another embodiment of the detector with a water permeable membrane,
- Fig. 17 shows a further development of the ATR needle probe detector with a glucose permeable membrane, and
- Fig. 18 shows a detector detecting the transmission of light through a
30 sample.

A light aggregate providing infrared light in selected wavelength bands is shown schematically in Fig. 1 wherein 2 is a source of wide-banded light and 1 is a concave mirror concentrating the light from the source 2 into a beam 20 of light which is passed through a beam splitting device comprising a semi-transparent reflecting surface 26a and a totally reflecting surface 26b. The two beams 20a, 20b of light provided in this way are transmitted through two different areas of a rotatable filter disc 4 which areas form filters f_1 - f_8 for measuring wave bands and a reference wave bands, respectively.

In the path of the two beams 20a and 20b a rotary diaphragm 3 is placed having its centre between the two beams and having a cut out sector. By rotating this diaphragm 3 the two light beams are chopped with the same frequency defined by the rotation speed of the diaphragm 3 and as indicated by the dotted circles the beams 20a and 20b are positioned such that the chopping of the respective beams will be out of phase. The aggregate is so designed that the two chopped beams are directed towards an optical coupling means 5 for coupling to the transmitting means transmitting the light to a sensor. The transmitting means may be an optical fibre or the transmission may take place directly through the air.

Fig. 2 shows another embodiment of the diaphragm 3. This diaphragm is designed to be rotated about a centre placed at one side of the two beams and it has two sets of apertures 6 each set being placed on a circle concentric with the diaphragm, the numbers of apertures and the radii of the circles being different for the respective sets. The difference of the radii is equal to the distance between the two beams of infrared light. In this way the two light beams may be chopped at different frequencies.

Fig. 3 schematically shows a detection device based on the attenuated total reflection (ATR) principle. From the coupling means 5 light is transmitted through an optical fibre 7, or fibre bundle through an optical device 27 directing the light from the fibre 7 through another optical fibre 28 to a single ended ATR needle probe 29. The reflected light passes through the fibre 28 and is in the device 27 directed through the fibre 10 to a detector 30. As the active area of the ATR needle is the outer surface a further embodiment of this device includes the ATR needle 29 having

a central canal as illustrated in Fig. 4. Fig. 5 shows a similar embodiment with the ATR needle 29 attached to a metal needle 24 for infusion of fluids.

In Fig. 6 an input fibre to the ATR-needle 29 comprises a number of fibres each connected to its individual semi-conductor thermal device 31. Monochromatic IR filters 32 between each thermal device 31 and its corresponding fibre allow each fibre in the bundle to carry a specific light wave band. A specific light wave band for the fibre may also be produced using a single thermal device 31 and a filter wheel. In another embodiment not shown the devices 31 may be narrow band light emitting diodes each emitting infrared light in a chosen band. In this case no monochromatic IR filters would be needed. The reflected light passes back up the core fibre of the bundle 33 to the detector 30.

The ATR needle 29 is inserted through the skin 8 into the subcutaneous tissue 17 as shown in Fig. 7. As shown in Figs. 4 and 5, the ATR-needle probe may have a canal for infusion of fluid or it may be attached to a needle for subcutaneous infusion of a fluid, e.g. insulin.

Fig. 8 shows a detector which may be used for non-invasive detection of the absorption of infrared light transmitted to the skin. The detector comprises a sensing chamber 15 and a reference chamber 16 and a differential pressure transducer 14 measuring the pressure difference between the chambers 15 and 16 and giving off an electric signal through leads 12, this signal being representative of the pressure difference. The reference chamber 16 has a screw 13 for adjusting the volume of the response by damping background noise.

Infrared light is transmitted from the light aggregate to the sensing chamber through an optical fibre 10 and will pass across the air space in the sensing chamber and into the skin.

As the beam of radiation passes through the skin into the underlying tissue certain molecules absorb radiation of specific wavelengths and convert it into heat. This heat then diffuses to the surface and heats the air in the chamber producing a pressure wave. The light which is pulsed stimulates cycles of heating and subsequent cooling in the skin which in turn produces pressure waves in the chamber at the same frequency as the pulses of light. This is detected by the

pressure transducer 14 and is converted into an electrical signal. The amplitude of the electrical signal is in proportion to the amount of heat produced which is proportional to the number of molecules or the concentration of that substance.

Pressure waves in the detector may be produced by sound waves arising from the body, and are therefore noise, reach both chambers and the pressure changes in both chambers therefore being equal do not move the transducer diaphragm placed between the chambers.

As the heat from the deeper layers will take longer to diffuse to the surface the delay in the signal can be used to relatively select out an area of the deeper layers of skin. In this way the concentration of the blood sugar in the vessels of the dermis can be measured.

In another embodiment shown in Fig. 9 infrared light is transmitted to both of the chambers of the detector, light of the sample wavelength being transmitted to one chamber 15 and light of the reference light wavelength being transmitted to the other 15a. The transducer 14 measures the pressure difference between the two chambers 15 and 15a and the response signal is led to a measuring device by leads 12.

By adjusting the light radiation of the reference and the sample beam such that the pressure difference between the two chambers is low when the concentration of the measured substance in the skin is low much improved sensitivity of the pressure transducer can be obtained by increasing the sensitivity of the pressure difference transducer.

In a further development of the above detector as shown in Fig. 10 two further pressure transducers 14a and 14b are added, at the end of the chamber lying opposite the transducer 14 between the chambers 15 and 15a and with their diaphragms lying in planes parallel with the plane of the diaphragm of the transducer 14. As the two further transducers 14a and 14b face each other their signals are opposite when their diaphragms are relatively moved due to movement of the total device in a direction perpendicular to the planes of the diaphragms.

The signals from the transducers 14a and 14b are amplified and balanced and electrically added to the signal from the differential pressure transducer 14 as

shown by the electrical diagram in Fig. 11. One of the signals from leads 12a and 12b is inverted and added to the other in the amplifier 34, and the added signal is added to the differential signal on the leads 12, amplified in an amplifier 35. By so doing the response in the chambers is increased and the noise due to horizontal
5 vibration reduced.

In the above embodiments the light is transmitted from a light aggregate to the detector through optical fibres or other kinds of light transmitting means. In another embodiment shown in Fig. 12 the light is generated in the detector by surface emitting light diodes 37 and 37a emitting infrared light at the sample
10 wavelength and the reference wavelength, respectively. From the light diodes 37 and 37a light passes over the space of the chambers 15 and 15a into the tissue 17. The pressure change produced is measured by the pressure transducer 14 and the response signal is carried by the leads 12 to a measuring and computing device.

The use of light emitting diodes will make the detector more mobile as only
15 electric connections to controlling means and to the measuring and calculating device will be necessary. Less mobile is a detector which further has to be connected to a light aggregate through an optical fibre. Embodiments using a conventional optical transmission will be immobile to an extent making it necessary to bring the measuring object to the device rather than bringing the detector to the
20 sampling spot of the patient.

With the above thermal detectors the relation between the response of the tissue to a sample wavelength and to its reference wavelength may be measured. The response may be measured for all the sample wavelengths and the reference wavelengths in sequence or overlapping in a way making it possible to discriminate
25 the individual relations.

Another way of performing a simultaneous measurement at two wavelengths, e.g. a sample wavelength and a reference wavelength and cancelling the effect of "lateral" movement is using a detector comprising a doubling of the device according to Fig. 9. In this way four chambers 115, 115a, 215 and 215a are provided as seen
30 in Fig. 13 showing the double detector seen from the bottom. The two sets of sample and reference wavelengths are transmitted to the respective detector units

through optical fibres and the response of the tissue to the two sets of wavelengths is measured by transducers 114 and 214. The detector units being oriented oppositely implies that signals from the two transducers 114 and 214 due to longitudinal vibrations could be added to each other and balanced out.

5 In the same way the detector of Figs. 9 to 12 may be triplicated to measure the relations of the responses to three pairs of wavelengths that are three pairs of sample wavelengths and reference wavelengths thus decreasing measuring time and eliminating noise from horizontal vibration. Such a triplicated detector is schematically shown seen from the bottom in Fig. 14. The sample and reference chambers have
10 the reference numbers 115, 215, 315 and 115a, 215a, 315a, respectively, infrared light being transmitted to each chamber through optical fibres. Each transmitting fibre carries an individual wavelength.

As collection of condensing water especially in a chamber to which infrared radiation is transmitted in a thermal detector of the kind described impairs the
15 measurement precautions should be taken to remove water and water vapour from such chambers. This may be done as sketched in Fig. 15 by providing compartments 38 communicating with the chamber to be dehydrated and place a desiccant in this compartment. Another possibility is as sketched in Fig. 16 to provide the chambers 15,15a with water permeable membranes 39 between the
20 inner of the chambers 15,15a, respectively, and the atmosphere.

The efficiency of the ATR needle probe 29 shown in Fig. 3 can be further enhanced by the addition of an extremely thin metal coating to be outside of the ATR needle (not shown) so as to make it act as a surface plasma resonance device. Fig. 17 illustrates a further embodiment of the ATR needle shown in Fig. 3. The
25 probe is jacketed by a glucose permeable membrane 40 with a space below 41 for fluid to collect between the membrane 40 and the ATR needle 29. Furthermore, the membrane may incorporate an enzyme (not shown) and ATR needle detector used to measure a product of that enzymic reaction in the fluid space 41.

Fig. 18 illustrates a further detector whereby the light is transmitted from a
30 coupling device (not shown) down an input optical fibre 7, through a lens (not shown) and reflected by mirror 42a across a gap 43 into which tissue fluid may

freely enter and the transmitted light is reflected by mirror 42b into the output optical fibre 10 and to a light detector (not shown).

CLAIMS

1. A method for in vivo measurement of the concentration of a substance, especially glucose, in the blood despite varying concentrations of interfering components, such as protein and fat, by measuring the absorption of selected
5 wavelengths of infrared light, characterized in that light of the selected wavelengths is selected from the range 1 - 40 μ m and is transmitted to the tissue of a person whose blood is being tested for its content of the substance, that at least one of the wavelengths is selected from the range 3 - 10 μ m, that the concentration is measured for the substance as well as for interfering components using for each substance or
10 component to be measured two different wavelengths of infrared light, one being a measuring wavelength at which the component or substance shows a specific absorption and the other being a reference wavelength at which the component or substance shows a low absorption, that a detector placed in or on the skin is used, and that the result of the measuring of the substance is corrected by taking into
15 account the absorption caused by the interfering components at the measuring and the reference wavelengths for the substance.

2. A method according to claim 1, characterized in that the light is transmitted to the tissue and the light absorption is measured by attenuated total reflection transcutaneously, i.e. invasively or non-invasively.

20 3. A method according to claim 1, characterized in that the light is transmitted to the outer side of the skin and the absorption is measured by detecting the heat generated in the tissue beneath the skin.

4. A method according to any of the preceding claims, characterized in that the light transmitted to the tissue is modulated.

25 5. A method according to claim 4, characterized in that different modulation frequencies are used for the light used for measuring the concentration of different components and substances.

6. A method according to claim 5, characterized in that the different modulation frequencies are not harmonic.

7. A method according to any of the claims 4 to 6, **characterized** in that the modulation of the measuring wavelength and the modulation of the reference wavelength are not in phase.

8. A method according to any of the claims 4 - 7, **characterized** in that the modulation is performed by chopping the light.

9. A method according to any of the preceding claims, **characterized** in that measured light absorptions are expressed as computable electrical signals, and that correction and interpretation of the measured values are made by calculation.

10. A method according to any of the preceding claims, **characterized** in that the substance the concentration of which is measured is glucose.

11. A method according to any of the preceding claims, **characterized** in that the substance the concentration of which is measured is CO₂

12. A method according to any of the preceding claims, **characterized** in that the substance the concentration of which is measured is ethanol.

13. A method according to any of the preceding claims, **characterized** in that the sample wavelength and the reference wavelength used for glucose are $9.5 \pm 0.5 \mu\text{m}$ and $7.7 \pm 0.5 \mu\text{m}$, respectively.

14. A method according to any of the claims 1-12, **characterized** in that the sample wavelength and the reference wavelength used for glucose are $3.47 \pm 0.5 \mu\text{m}$ and $2.96 \pm 0.5 \mu\text{m}$, respectively.

15. A method according to any of the preceding claims, **characterized** in that the sample wavelength and the reference wavelength for fat are $5.74 \pm 0.5 \mu\text{m}$ and $5.58 \pm 0.5 \mu\text{m}$, respectively.

16. A method according to any of the claims 1-14, **characterized** in that the sample wavelength and the reference wavelength for fat are $3.513 \pm 0.5 \mu\text{m}$ and $3.57 \pm 0.5 \mu\text{m}$, respectively.

17. A method according to any of the preceding claims, characterized in that the sample wavelength and the reference wavelength for protein are $6.5 \pm 0.5 \mu\text{m}$ and $6.7 \pm 0.5 \mu\text{m}$, respectively.

18. An apparatus for carrying out the method according to any of the claims 5 1 - 17 for in vivo measurement of the concentration of a substance, especially glucose, in the blood despite varying concentrations of interfering components, such as protein and fat, by measuring the absorption of selected wavelengths of infrared light, characterized in that it comprises a light aggregate able to provide selectable narrow light bands in the wavelength range of 1 - $40 \mu\text{m}$ whereof at least one band 10 lies in the range of 3 - $10 \mu\text{m}$, means for transmitting light from the aggregate to the tissue of a person whose blood or tissue fluid is being measured for its content of the substance, a detector designed to be placed in or on the skin and detecting the absorption of light in the the tissue by providing electric signals representative of the absorption detected, and a computer calculating the concentration of the substance 15 on the basis of the detected absorption values.

19. An apparatus according to claim 18, characterized in that the light aggregate comprises a wide-banded light source and a number of filters each transmitting one of the selected narrow light bands.

20. An apparatus according to claim 18, characterized in that the light 20 aggregate comprises a number of surface emitting light diodes each emitting infrared light of a chosen wavelength.

21. An apparatus according to claim 18, 19 or 20, characterized in that the light aggregate comprises means for focussing the light on an optical coupling means for the light transmitting means.

22. An apparatus according to any of the claims 18 - 21, characterized in that 25 the light aggregate comprises chopper means for chopping at preset chopping frequencies the light wave bands transmitted from the light aggregate.

23. An apparatus according to claim 22, characterized in that the chopper means is a rotating diaphragm with cut-outs.

24. An apparatus according to claims 20 and 22, characterized in that the chopper means is an electronic circuit controlling the energization of the light diodes or semiconductor sources.

25. An apparatus according to any of the preceding claims, characterized in
5 that the detector comprises an optical needle probe ATR cell having an input fibre and an output fibre, and at the output fibre a light detector providing an output signal, representing by an electric signal the light absorption measured.

26. An apparatus according to any of the claims 18 - 24, characterized in that
10 the detector comprises a pair of chambers having an open side placed against the skin at the measuring spot, and a pressure transducer measuring the pressure difference between the chambers representing this differential pressure by an electric signal.

27. An apparatus according to claim 26, characterized in that the one
15 chamber at its side opposite the open side has an inlet for infrared radiation transmitted from the light aggregate.

28. An apparatus according to claim 26, characterized in that both chambers
have at their sides opposite the open sides inlets for infrared radiation transmitted from the light aggregate.

29. An apparatus according to claim 28, characterized in that a further
20 transducer is added to each chamber at the ends thereof and with its diaphragm lying in a plane-parallel with the plane of the diaphragm of the transducer between the chambers.

30. An apparatus according to any of the claims 26 - 29, characterized in that
25 each chamber having an inlet for infrared radiation communicates with a compartment containing a desiccant.

31. An apparatus according to any of the claims 26-29, characterized in that
each chamber having an inlet for infrared radiation has a wall with a rigid water permeable membrane.

32. An apparatus according to claim 25, characterized in that the ATR needle
30 probe cell is coated with a metal such that it acts as a surface plasma resonance device.

33. An apparatus according to claim 32, characterized in that the metal coated ATR needle probe may be jacketed by a cellulose permeable membrane with a gap between the membrane and the probe.

34. An apparatus according to claim 33, characterized in that the membrane
5 may have a glucose specific enzyme or system of enzymes and the ATR probe used to measure the product of enzymic reaction of the glucose molecule.

35. An apparatus according to claims 18-24, characterized in that the detector
comprises an optical device with input and output optical fibres with an optical
element comprising a sample space for a fluid sample and a transmission
10 measurement made of that sample.

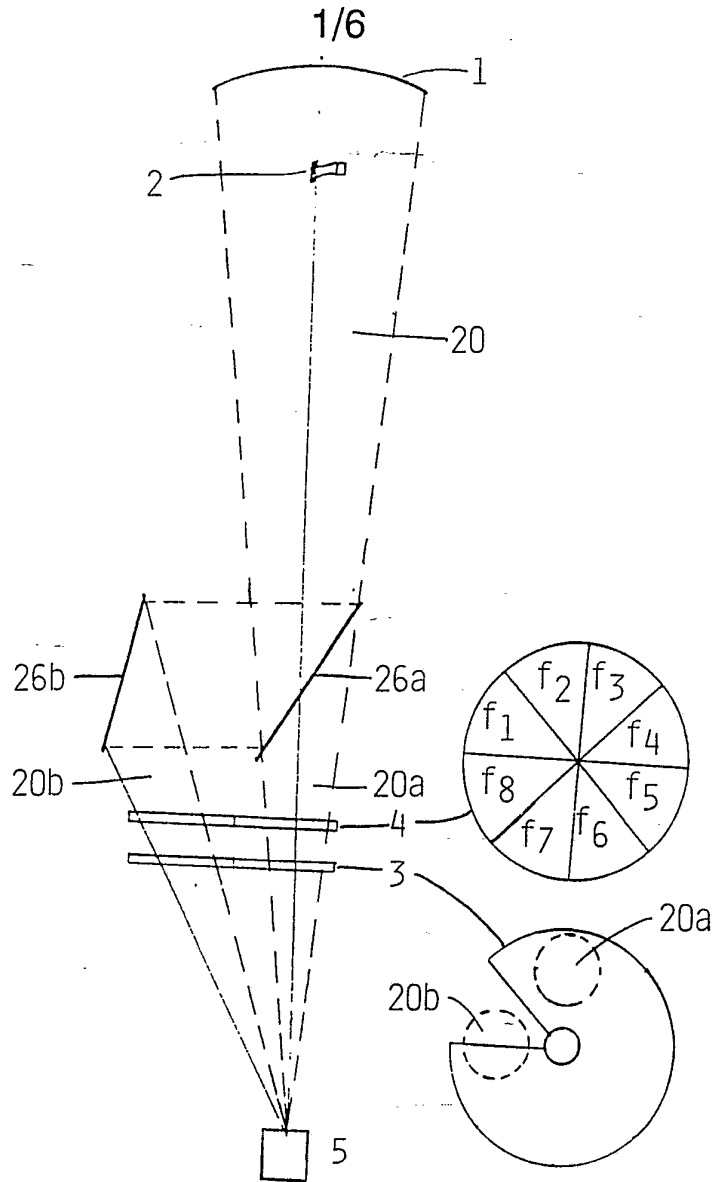


Fig. 1

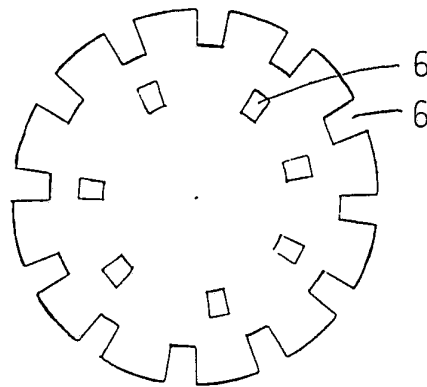


Fig. 2

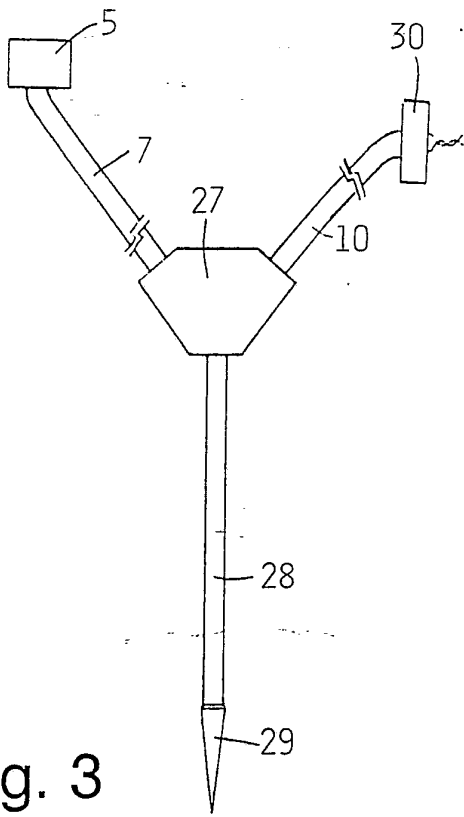


Fig. 3

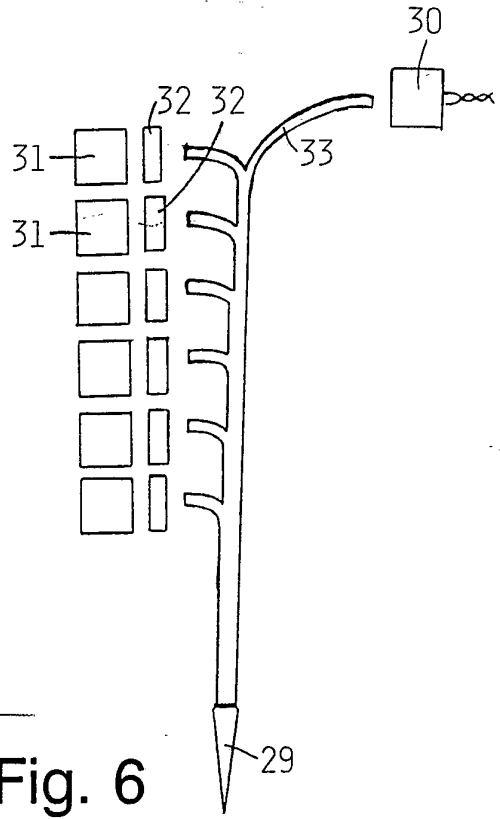


Fig. 6

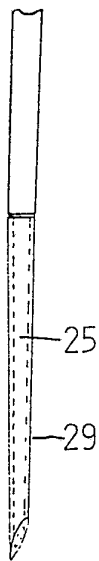


Fig. 4

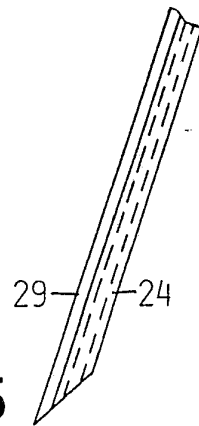


Fig. 5

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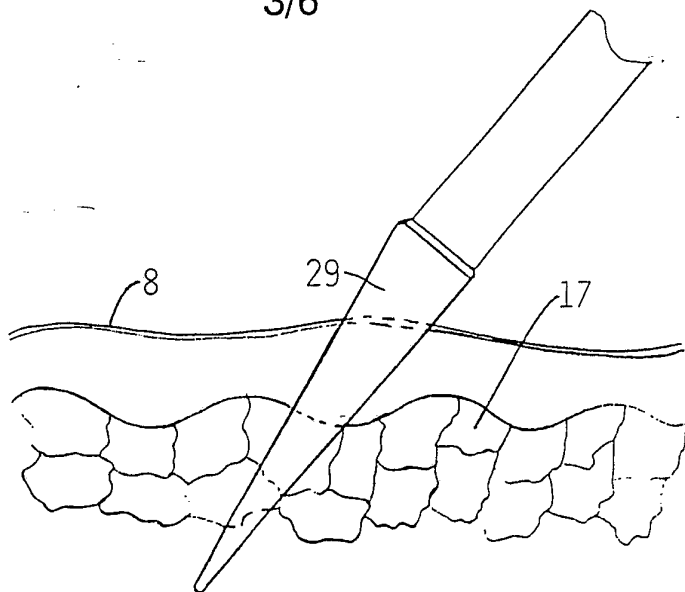


Fig. 7

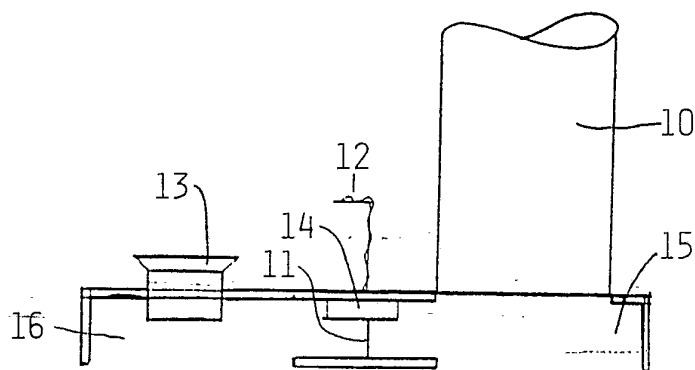


Fig. 8

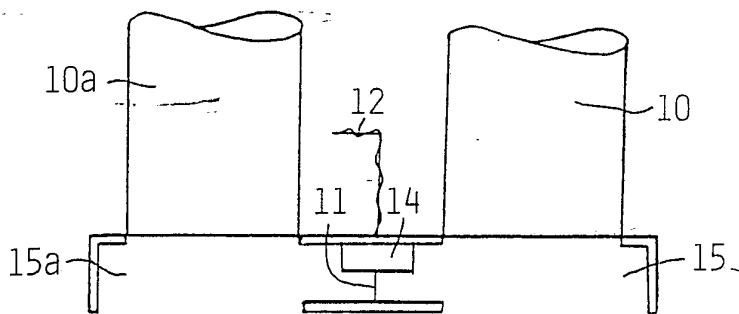


Fig. 9

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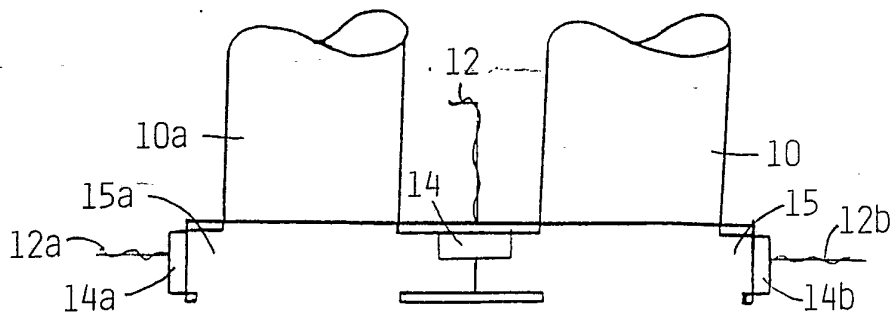


Fig. 10

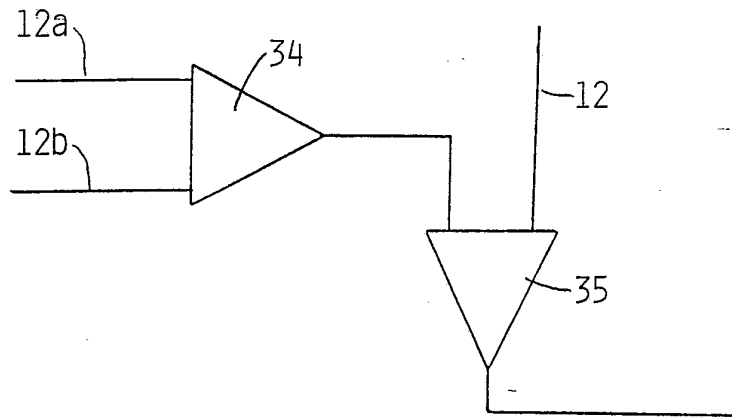


Fig. 11

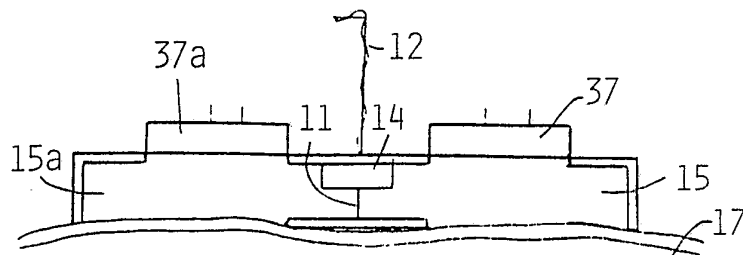


Fig. 12

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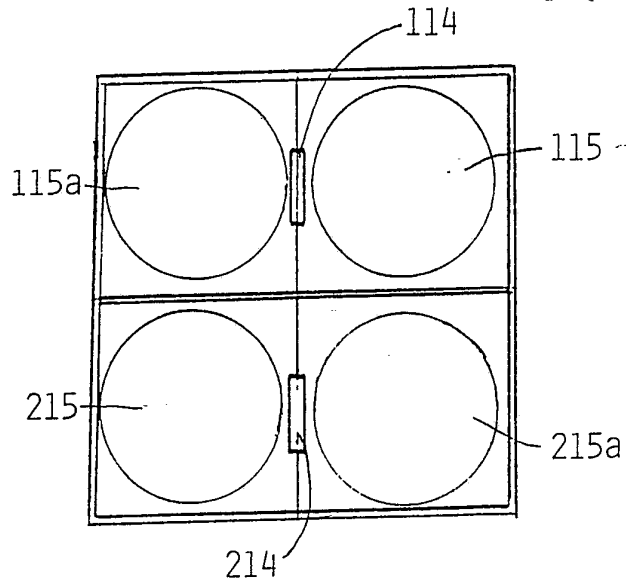


Fig. 13

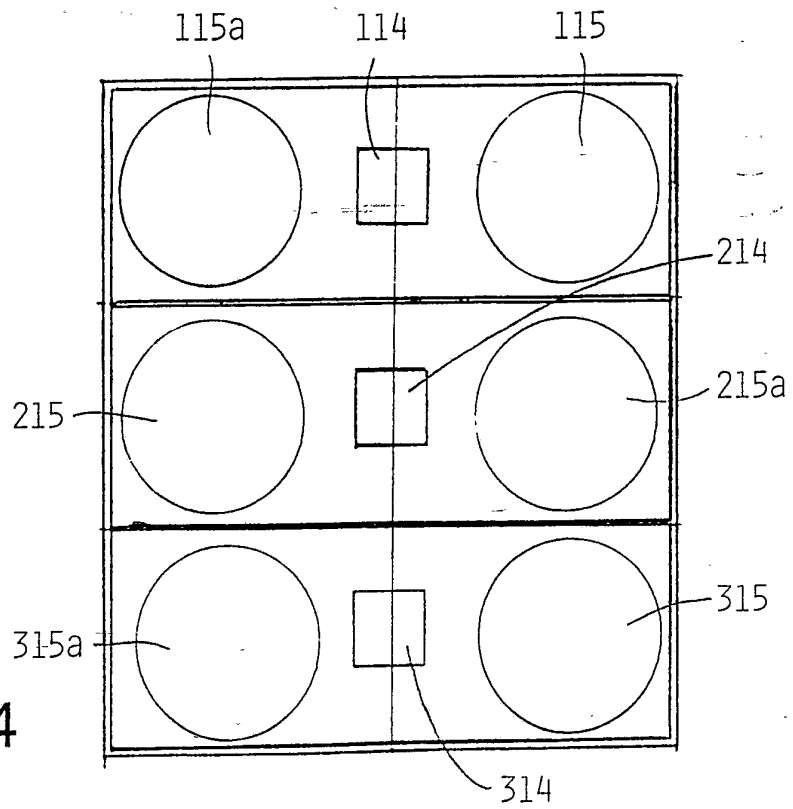


Fig. 14

Fig. 15

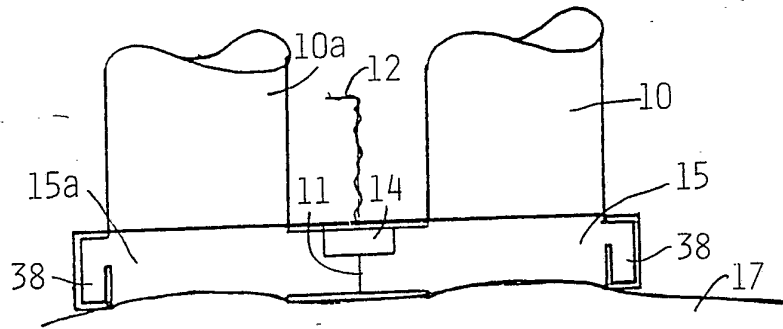


Fig. 16

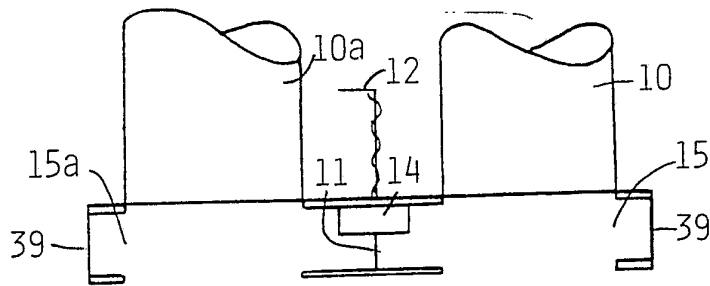


Fig. 17

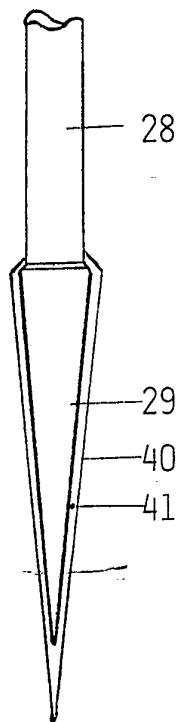
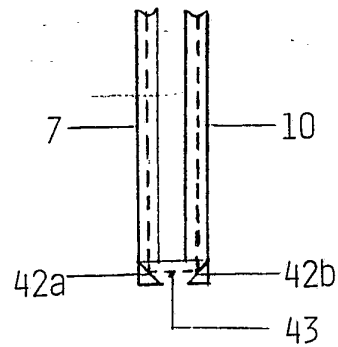
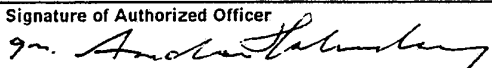


Fig. 18



INTERNATIONAL SEARCH REPORT

International Application No **PCT/DK 91/00152**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC5: A 61 B 5/00; A 61 B 5/14; G 01 N 21/35		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	A 61 B; G 01 N	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US, A, 4882492 (K. J. SCHLAGER) 21 November 1989, see column 3, line 45 - column 4, line 27; abstract; figure 1	18-24
Y		1-2
A	--	3-17, 25 -35
Y	US, A, 4655225 (C. DÄHNE ET AL) 7 April 1987, see column 3, line 34 - column 4, line 5; column 6, line 61 - column 7, line 4; abstract	1-2
A	--	3-35
A	US, A, 4509522 (T. J. MANUCCIA ET AL) 9 April 1985, see column 2, line 25 - line 50; column 3, line 39 - line 63; abstract	1-35
	--	
<p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
24th September 1991	1991 -09- 30	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	 KARIN SÄFSTEN Anders Holmberg	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4427889 (G.J. MÜLLER) 24 January 1984, see abstract ----- -----	1-35

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 91/00152**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **91-08-30**. The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4882492	89-11-21	NONE	
US-A- 4655225	87-04-07	NONE	
US-A- 4509522	85-04-09	NONE	
US-A- 4427889	84-01-24	DE-A- 2934190	81-03-19
		EP-A-B- 0034156	81-08-26
		WO-A- 81/00622	81-03-05