

- [54] **BLOOD ANALYZER**
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- [63] Continuation of Ser. No. 4,983, Jan. 22, 1970, abandoned.
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[51] Int. Cl. **G01n 31/00, G01n 33/16**
[58] Field of Search **23/230 B, 253 R; 210/22**

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[57] **ABSTRACT**

A pair of syringes respectively coupled by way of a pair of three-way valves to a source of blood and a source of reagent, so that withdrawing the plungers fills the syringes respectively with blood and reagent. The three-way valves are switched and a motor mechanism is activated simultaneously to move the plungers into the syringes to move the blood and the reagent through a pair of chambers separated by a semi-permeable membrane. A selected substance in the blood is dialyzed through the membrane and reacts with the reagent to furnish a product, the concentration of which is measured to determine the concentration of the selected substance in the blood.

4 Claims, 11 Drawing Figures

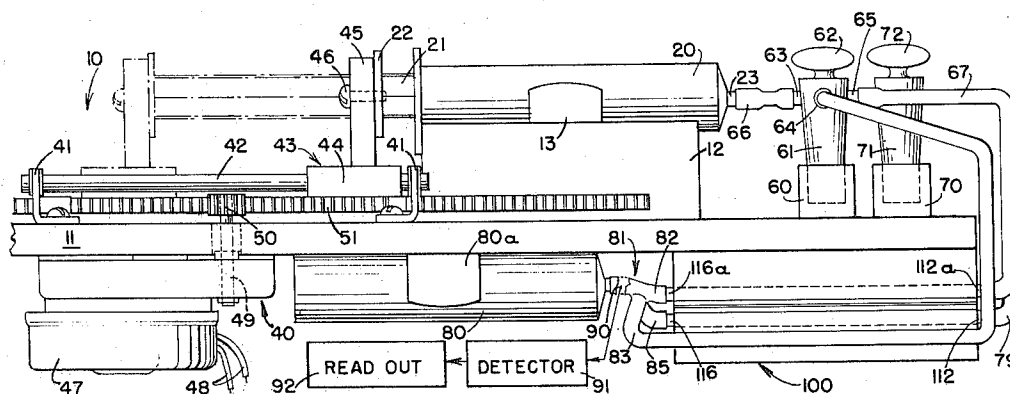


FIG. 1

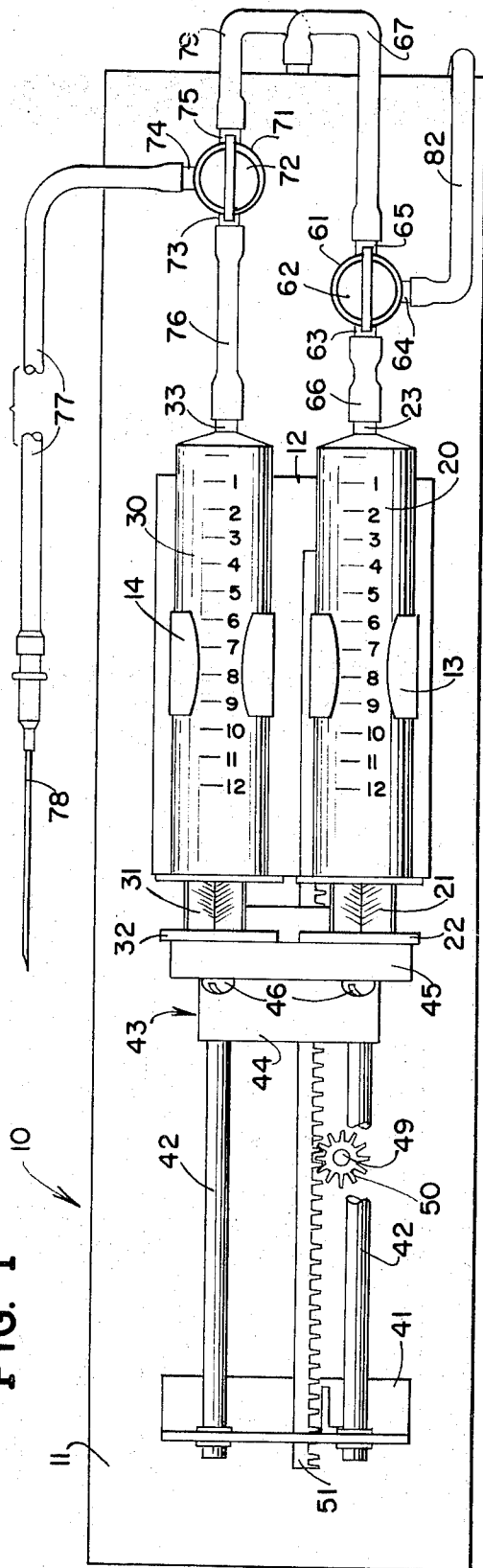
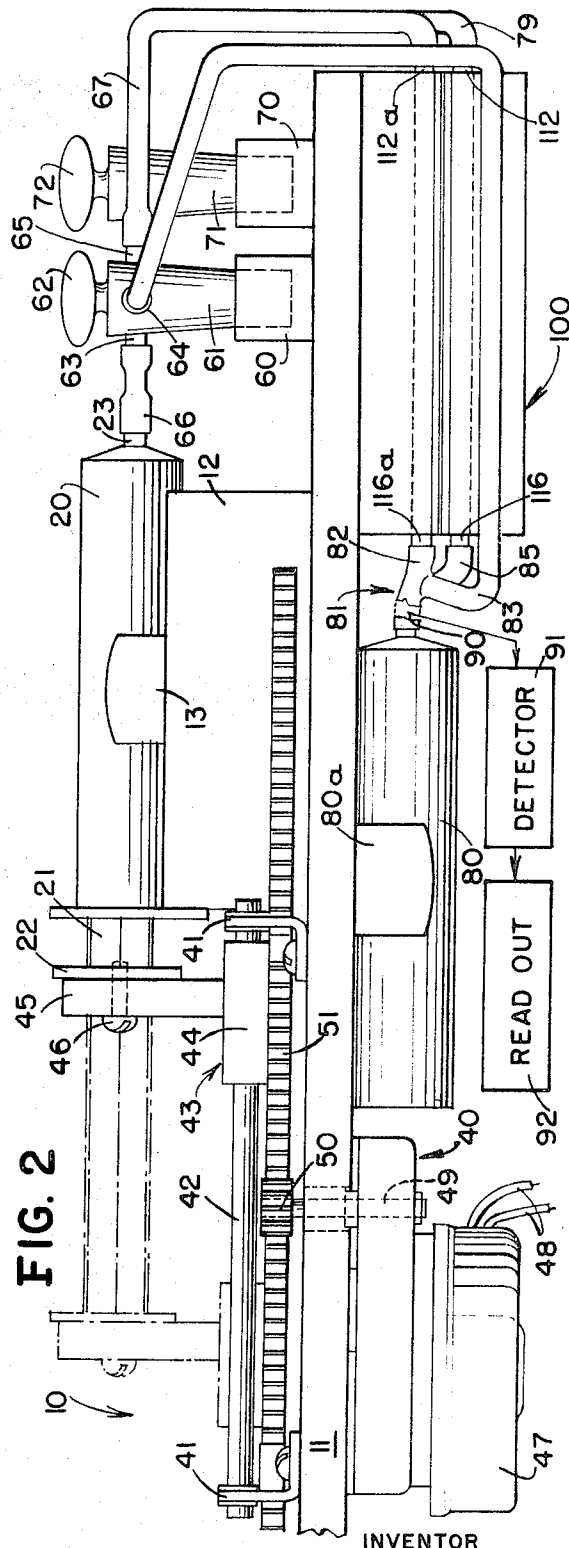
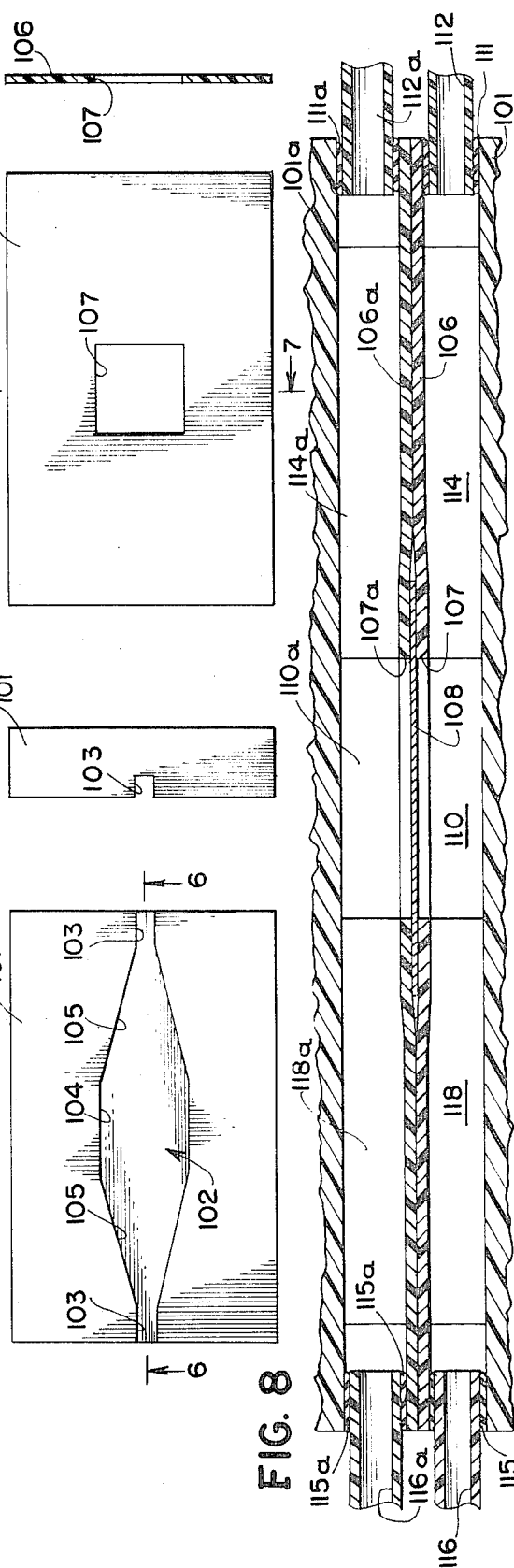
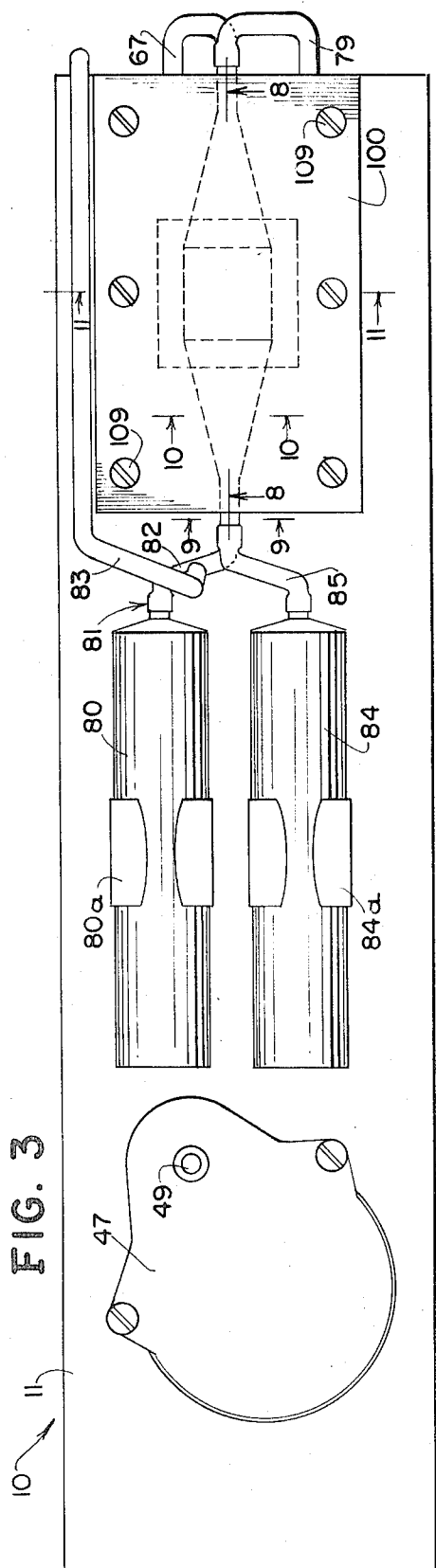
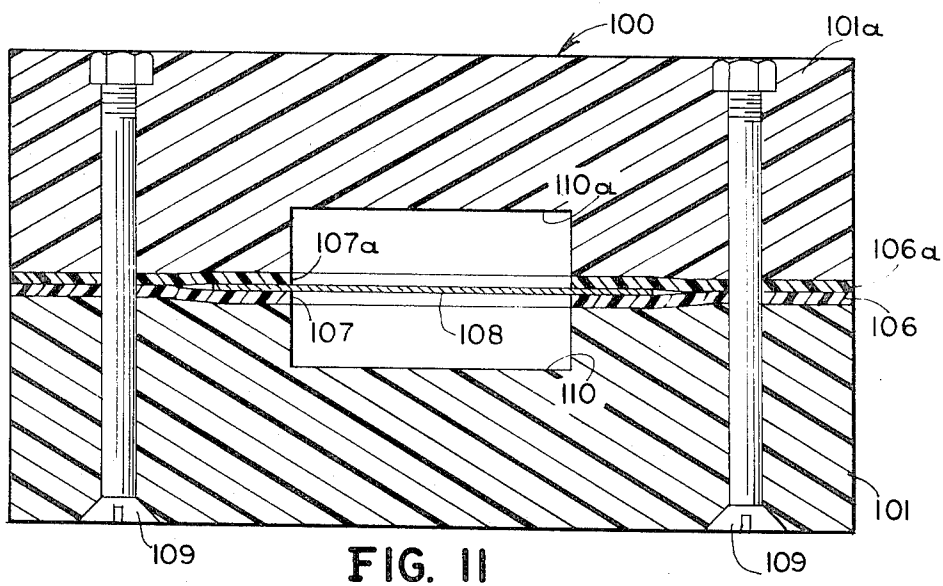
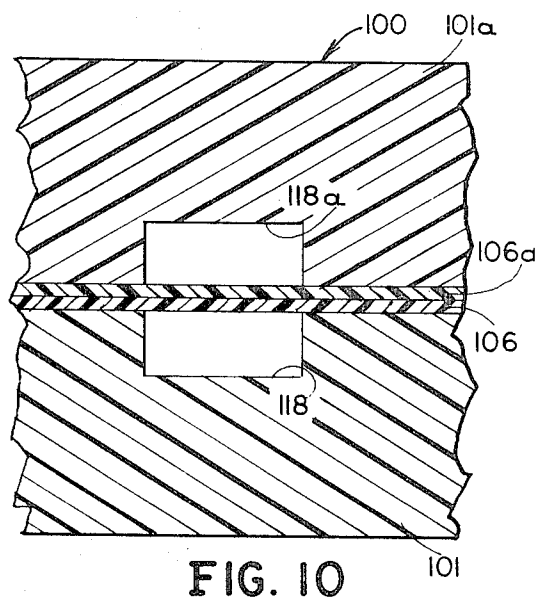
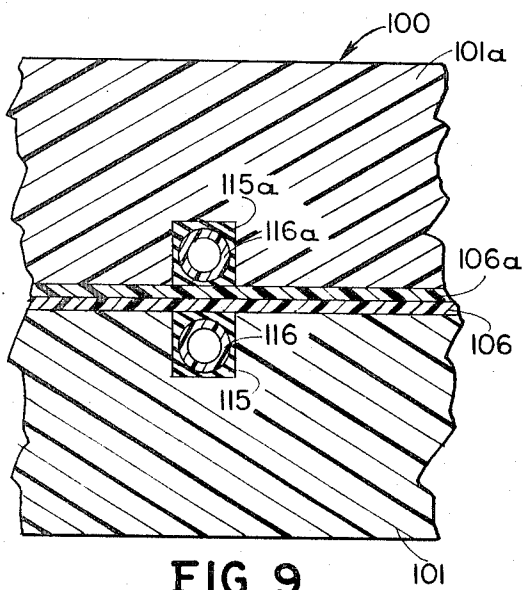


FIG. 2



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BLOOD ANALYZER

This is a continuation application of Ser. No. 4,983 filed Jan. 22, 1970, now abandoned.

It is an important object of the present invention to provide a blood analyzer both to withdraw a blood specimen and to analyze it essentially in the same time it now takes for a technician just to withdraw the blood.

Another object of the present invention is to provide a blood analyzer which, after determining the concentrations of various substances in the blood, furnishes a container of blood for further use as desired.

Still another object of the present invention is to reduce the cost of making blood tests.

Yet another object of the present invention is to provide a blood analyzer which produces a product, the concentration of which is directly proportional to the concentration of a selected substance in the blood.

A further object is to provide a portable blood analyzer capable of both withdrawing a blood sample and analyzing it.

In summary, there is provided a blood analyzer for use with a source of reagent capable of reacting with a selected substance in blood to provide a product proportional in concentration to the concentration of the selected substance, the analyzer comprising a pair of syringes each having a movable plunger, a separating device including a conduit and a semipermeable membrane dividing the conduit into a pair of chambers each having an inlet and an outlet, a pair of three-way valves respectively having first ports respectively coupled to the sources of blood and reagent and second ports respectively coupled to the syringes and third ports respectively coupled to the inlets of the chambers, each of the valves having a first condition wherein the first and second ports thereof are in communication and the third port is blocked and a second condition wherein the second and third ports are in communication and the first port is blocked, the plungers being withdrawn while the valves are in the first condition thereof to draw into one of the syringes a quantity of the blood and into the other of the syringes a quantity of the reagent, a driving device for simultaneously moving the plungers into the syringes while the valves are in the second condition thereof to move the quantities of blood and reagent respectively through the chambers, whereby the selected substance in the blood is dialyzed through the semipermeable membrane and reacts with the reagent to furnish a product proportional in concentration to the concentration of the selected substance in the blood, and a sensing device coupled in the path of the reagent having the selected substance therein and operative to indicate the concentration of the product in the reagent and thus the concentration of the selected substance in the blood.

With the foregoing and other objects in view which will appear as the description proceeds, the invention consists of certain novel features of construction, arrangement and a combination of parts hereinafter fully described, illustrated in the accompanying drawings, and particularly pointed out in the appended claims.

For the purpose of facilitating an understanding the invention, there is illustrated in the accompanying drawings the preferred embodiment thereof, from an inspection of which, when considered in connection with the following description, the invention, its mode of construction, assembly and operation, and many of

its advantages should be readily understood and appreciated.

Referring to the drawings in which the same characters of reference are employed to indicate corresponding or similar parts throughout the several figures of the drawings:

FIG. 1 is a top plan view of a blood analyzer incorporating the features of the present invention;

FIG. 2 is a side elevational view of the blood analyzer of FIG. 1;

FIG. 3 is a bottom plan view of the blood analyzer of FIG. 1;

FIG. 4 is a plan view of one of the elements of the separating device in the blood analyzer;

FIG. 5 is an end elevational view of the element of FIG. 4;

FIG. 6 is a plan view of another element in the separating device;

FIG. 7 is a cross-sectional view of the element shown in FIG. 7, taken along the lines 7—7 thereof;

FIG. 8 is an enlarged cross-sectional view of the separating device, taken along the lines 8—8 in FIG. 3;

FIG. 9 is an enlarged cross-sectional view of the separating device, taken along the lines 9—9 in FIG. 3;

FIG. 10 is an enlarged cross-sectional view of the separating device taken along the lines 10—10 in FIG. 3; and

FIG. 11 is an enlarged cross-sectional view of the separating device, taken along the lines 11—11 in FIG. 3.

Referring now to the drawings, there is shown a blood analyzer 10 incorporating therein the novel features of the instant invention. The blood analyzer 10 is provided with a base 11 which, in the form shown, is an elongated rectangular slab constructed of plastic. Fastened onto the base 11 is a syringe support 12 which, in turn, has mounted thereon a pair of laterally-spaced apart clamps 13 and 14. Snap-fitted into the clamp 13 is a syringe 20 which is of standard construction in the medical field. The syringe 20 includes a plunger 21 carrying on the outer end thereof a head 22, the forward portion of the syringe 20 having a nose 23, as is usual. A second syringe 30 disposed parallel to the syringe 20 is snap-fitted into its clamp 14 and is essentially of the same construction as the syringe 20, having a plunger 31 which carries a head 32, the front of the syringe 30 being provided with a nose 33. The clamps 13 and 14 enable the technician to remove and replace the syringes 20 and 30 at will.

The blood analyzer 10 further comprises a driving assembly designated generally by the numeral 40. The driving assembly includes a pair of longitudinally-spaced-apart rails 42 and a carriage 43 which is defined by a horizontally-disposed table 44 and an upstanding plate 45. Formed in the table 44 is a pair of laterally-spaced-apart bores (not shown) respectively receiving the rails 42, which, in the form shown, are round. The rails 42 thus provides a guide along which the carriage 43 is longitudinally movable. A pair of screws 46 interconnect the upstanding plate 45 respectively with the heads 22 and 32. As can be best seen by the phantom lines in FIG. 2, longitudinal movement of the carriage 43 results in corresponding simultaneous longitudinal movement of both the plungers 21 and 31.

The driving assembly 40 further includes a motor 47 suitably bolted to the underside of the base 11 and having wires 48 connectable to a source of power. The

shaft 49 of the motor 47 passes through a bearing (not shown) mounted in an opening in the base 11 and protrudes upwardly therefrom. The outer end of the shaft 49 carries a pinion 50 which engages a rack 51, the rack, in turn, being suitably secured to the underside of the carriage table 44. The motor 47 is so constructed that, when de-energized, the shaft 49 is free to rotate counterclockwise, as viewed in FIG. 1, and, when energized, is rotated clockwise, as viewed in FIG. 1. Thus, when the motor 47 is de-energized, the user can grasp the carriage 43 and move it rearwardly to withdraw the plungers 21 and 31. He can then energize the motor 47 to cause the pinion 50 to rotate clockwise, to move the rack 51 forwardly and thereby carry into their respective syringes 20 and 30 the plungers 21 and 31.

Also mounted on the upper side of the base 11 is a pair of sockets 60 and 70 respectively mounting a valve seat 61 and a valve seat 71 and associated valves 62 and 72. The valve seat 61 is a three-way device, having a first port 63, a second port 64, and a third port 65. The valve 62 is rotatable in the valve seat 61, so that it may be placed in a first condition wherein the port 64 communicates with the port 63 to accommodate fluid flow therebetween and the port 65 is blocked; and so that it may be placed in a second condition wherein the port 65 communicates with the port 63 to accommodate fluid flow therebetween and the port 64 is blocked. The port 63 is coupled to the nose 23 of the syringe 20 by means of rubber tubing 66. The port 65 is coupled to one inlet of a separating device 100, the construction of which will be explained in detail hereinafter.

The valve seat 71 also has three ports 73, 74, and 75, the port 73 being coupled to the nose 33 of the syringe 30 by means of rubber tubing 76. The valve 72 is rotatable in the valve seat 71, so that it may be placed in a first condition wherein the port 74 communicates with the port 73 to accommodate fluid flow therebetween and the port 75 is blocked, and so that it may be placed in a second condition wherein the port 75 communicates with the port 73 to accommodate fluid flow therebetween and the port 74 is blocked. The second port 74 is coupled by way of a tubing 77 to a hypodermic needle 78, and which needle is insertable in the circulatory system of the patient in the usual manner. The port 75 is coupled to a second inlet of the separating device 100 by means of rubber tubing 79.

Disposed beneath the base 11 and removably held in place thereon by means of a pair of clamps 80a and 84a is a pair of containers 80 and 84. One outlet of the separating device 100 is coupled to the container 80 by means of one branch 82 of a length of rubber tubing 81, and the other outlet is coupled to the container 84 by means of rubber tubing 85. The container 80 is coupled to the port 64 of the valve seat 61 by means of the branch 83 of the length of rubber tubing 81.

In use, a container 80 filled with a fresh reagent is snapped into the clamp 80a and an empty container 84 is snapped into the clamp 84a. The valves 62 and 72 are placed in their first conditions, and the plungers 21 and 31 are disposed well within their respective syringes 20 and 30. The technician grasps the carriage 43 and pulls it rearwardly to withdraw the plungers 21 and 31 and thereby fill the syringe 20 with the reagent from the container 80 and to fill the syringe 30 with blood from the patient's circulatory system. This movement is reasonably rapid and, as explained previously, is not inhibited by the motor 47. Upon completion of the strokes

of the plungers 21 and 31, the valves 62 and 72 are rotated into their respective second conditions, and the motor 47 is energized. Accordingly, the pinion 50 will rotate and move the rack 51 forwardly at a given velocity to move the plungers 21 and 31 into their respective syringes 20 and 30 at that velocity. The quantity of reagent in the syringe 20 moves through the tubing 66 and the tubing 67 into one inlet of the separating device 100, and the quantity of blood moves through the tubing 76 and the tubing 79 into the second inlet of the separating device 100. The quantities of blood and reagent move through the separating device 100 at the same flow rate and, as will be explained in detail hereinafter, the substance in the blood to be analyzed will react with the reagent. The effluent from an outlet of the separating device 100 consists of blood which fills the container 84. The effluent from the other outlet of the separating device 100 consists of a product representative of the concentration of the selected substance in the blood plus the used reagent which fills the container 80. A probe 90 is located in the path of the product flowing into the container 80 and is coupled to a detector 91 which, in combination with a read-out device 92, indicates the concentration of the selected substance in the blood. The container 80, which is now filled with used reagent, may be discarded and replaced by a container of fresh reagent for use in the next blood analysis. The container 84, filled with blood, can either be discarded or used for further analysis, if desired.

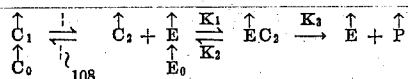
Referring now to FIGS. 4 to 7, the details of the separating device 100 will be described. In FIGS. 4 and 5 there is shown a block 101 which may be formed of plastic. Milled out of the block 101 is a complex cavity 102 having a constant depth. The cavity 102 includes a pair of narrow portions 103 adjacent to the ends of the block 101, a wide portion 104 located centrally, and a pair of flared portions 105 joining the narrow portions 103 to the wide portion 104. In forming the separating device 100, there is provided a second block 101a, which is essentially a duplicate of the block 101. As shown in FIGS. 6 and 7, the separating device 100 also includes a plate 106 having centrally therein a square window 107. The length of the window 107 is equal to the length of the wide portion 104 in the block 101, and the width of the window 107 is equal to the width of the wide portion 104. Another plate 106a of essentially the same construction is provided.

Referring now to FIGS. 8 to 11, the details of the separating device 100, as assembled, will be described. The plates 106 and 106a are secured together with a semipermeable membrane 108 mounted therebetween in registry with the windows 107 and 107a. The secured-together plates 106 and 106a are disposed between the two blocks 101, having their cavities 102 and 102a in facing relationship. The windows 107 and 107a in the plates 106 and 106a are in exact registry with the wide portions 104 and 104a of the cavities 102 and 102a. The two blocks 101 and 101a and the plates 106 and 106a are secured together by a set of six (See FIG. 3) fasteners 109. The space between the wide portion 104 of the cavity 102 and the membrane 108 defines a first chamber 110 and the portion between the membrane 108 and the wide portion 104a of the cavity 102a defines a second chamber 110a. The space defined by one (the one to the left as viewed in FIG. 8) of the narrow portions 103 and the adjacent plate 106 has mounted therein an outlet tube 116 surrounded by a

seal 115. Similarly, there is mounted in the space defined by the narrow portion 103a and the plate 106a an outlet tube 116a surrounded by a seal 115a. The tubes 116 and 116a protrude outwardly from the blocks 101 and 101a. Similarly, inlet tubes 112 and 112a are mounted in the narrow portions 103 at the other ends of the cavities in the blocks 101 and 101a, seals 111 and 111a respectively surrounding the tubes 112 and 112a.

The separating device 100 is mounted on the underside of the base 11 as previously explained, with the inlet tubes 112 and 112a facing the right and respectively connected to the tubing 79 and 67. The outlet tubes 116 and 116a are respectively coupled to the tubing 85 and the branch 82 of the tubing 81. When the valves 62 and 72 are placed in their second conditions and the motor is energized to move the plungers 21 and 31 into their respective syringes 20 and 30, the blood travels through the tubing 76 and 79, through the inlet tube 112, and the flared channel 114 into the chamber 110, where the blood is moved at a given flow rate past one surface of the semipermeable membrane 108. Simultaneously, the reagent in the syringe 20 is moved through the tubing 66 and 67, through the inlet tube 112a and the flared channel 114a and into the chamber 110a, wherein the reagent is moved past the outer surface of the membrane 108 at the same flow rate. The dialyzable substance in the blood in the chamber 110 passes through the membrane 108 and into the chamber 110a where it reacts with the reagent. The probe 90, the detector 91, and the read-out device 92 cooperate to measure the concentration of the product which, in turn, is converted into an indication of the concentration of the selected substance in blood. The blood then travels through the flared channel 118, through the outlet tube 116 and into the container 84. The used reagent and the product travel through the flared channel 118a, through the outlet tube 116a and into the container 80. The flared channels 114, 114a, 118 and 118a minimize turbulence in the blood and the reagent as they flow past the membrane 108.

The selected substance in the blood passes through the membrane 108 according to the following flow equation:



wherein C_0 represents the concentration of the selected substance in the blood to be analyzed, C_1 represents the concentration of that substance after time t in the chamber 110, C_2 represents the concentration of that substance after time t in the chamber 110a, E_0 represents the concentration of the enzyme in reagent, E represents the concentration of the reagent after time t in the chamber 110a, P represents the concentration of the product formed after time t in the chamber 110a, and K_1 , K_2 and K_3 are rate constants dependent upon the identity of the enzyme.

It can be shown that the product P has a concentration directly proportional to the concentration C_0 of the substance in the blood. Thus, by measuring the concentration of the product P and properly calibrating the detector 91 and the read-out device 92, a measurement of the concentration of the substance in the blood can be obtained. The following is the derivation of the for-

mula relating the concentration of the product to the concentration of the desired substance in the blood:

The Michaelis-Menten equation for determining the velocity v of an enzymatic reaction is:

$$v = (K_3 E_0 C_2 / C_2 + K_m) \quad (1)$$

wherein K_m is a constant dependent upon the identity of the enzyme.

The rate of formation of C_2 with respect to time t is:

$$(dC_2/dt) = j - (C_2 F/V) - v$$

wherein J represents the flux of the substance C_1 across the semipermeable membrane 108, F represents the flow rate of the blood through their respective chambers, and V represents the volume of the chamber 110.

An application of Fick's first law states that:

$$j = (DA/LV)(C_1 - C_2) \quad (3)$$

wherein D represents the diffusion coefficient of the substance in blood, A represents the cross-sectional area of the semipermeable membrane 108, and L represents the thickness of the membrane.

Conservation of mass requires that:

$$C_0 = C_1 + C_2 + P \quad (4)$$

Substituting equations (3) and (4) into equation (2):

$$(dC_2/dt) = (DA/LV)(C_0 - 2C_2 - P) - (C_2 F/V) - v \quad (5)$$

The rate of formation of P is:

$$(dP/dt) = v - (PF/V) \quad (6)$$

wherein F represents the flow rate of the reagent through the chamber 110a and V represents the volume of the chamber 110a, it being assumed in this derivation that the flow rates of the blood and reagent and the volumes of the chambers 110 and 110a are the same.

Assuming (F/V) is many times greater than $(2DA/LV)$, and solving the equations (1), (5), and (6) for P , the following result is obtained:

$$P = \frac{DAC_0}{LF} \left[\frac{1}{1 + \left(\frac{K_m}{K_3 E_0} \right) \left(\frac{F}{V} \right)} \right] \left(1 - e^{-\frac{Ft}{V}} \right) \quad (7)$$

It is desirable that equilibrium be 99 percent completed in less than three minutes, which requires that:

$$1 - e^{-180F/V} = 0.99 \quad (8)$$

and it is, therefore, necessary that F be greater than V . Preferably, equilibrium is to be achieved in 30 seconds, which requires F to be greater than $0.17 V$. Also, in order to maximize the sensitivity of the apparatus, it is desirable that the second term in equation (7) be ap-

proximately equal to 1.0, which requires that $(K_3 E_0 / K_m) \gg (F/V)$

Accordingly:

$$P = (DAC_0 / LF) \quad (9)$$

The dimensions of the chambers 110 and 110a were obtained as follows. Assuming equilibrium has been reached, differentiating P with respect to the area, and obtaining the maximum:

$$(dA/dV) = [AV/V + (K_m F / K_3 E_0)] \quad (10)$$

Again assuming $(K_3 E_0 / K_m) \gg (F/V)$, then:

$$(dA/dV) = A \quad (11)$$

Since $V = Az$, wherein z is the width of each chamber:

$$(dA/dV) = (1/Z) \quad (12)$$

Setting equations (11) and (12) equal to each other,

$$V = Az = 1.0. \quad (13)$$

Substituting equation (13) into equation (7) after equilibrium:

$$P = \frac{DC_0}{LzF} \left(\frac{1}{1 + \frac{K_m F}{K_3 E_0}} \right)^2 \quad (14)$$

Differentiating P with respect to F , setting (dP/dF) equal to zero, and assuming $K_3 E_0 / K_m \gg F/V$ and solving for Fz :

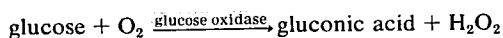
$$Fz = (K_m / K_3 E_0)^2 \quad (15)$$

Substituting equation (16) into equation (14) and assuming $(K_3 E_0 / K_m)$ is many times greater than F :

$$P = (DC_0 / L)(K_3 E_0 / K_m)^2 \quad (16)$$

Equation (13) expresses the fact that the maximum product P , and thus the greatest efficiency, occurs for unity volume. In one form of the invention, the area of each of the chambers 110 and 110a, as measured in a plane parallel to the membrane 108, was selected as 2 sq. cm., with each of the sides being 1.4 cm. in length. Thus, the area of the window 107 in the plate 106 and the area of the window 107a in the plate 106a were each 2 sq. cm., and measured 1.4 cm. on a side. The width of each of the chambers 110 and 110a was 0.5 cm. Thus, the depth of the cavity 102 in the block 101 and the depth of the corresponding cavity in the block 101a was 0.5 cm. In this form, therefore, the volume of the chamber 110 and the volume of the chamber 110a were unity (1).

In analyzing the blood to determine the concentration of glucose, the enzyme glucose oxidase may be used in the reagent according to the following equation: For glucose oxidase, the reaction will be:



in which case $K_3 = 0.00372$ mol./min./mg. and $K_m = 0.003$ mols./liter. The diffusion constant D for glucose

is 7×10^{-6} sq. cm./sec. In an operative form of the invention, the thickness L of the membrane 108 was 0.01 cm. For equilibrium to be 99 percent completed in 60 seconds, it is necessary for the third term in equation (7), $1 - e(-60t/V) = 0.99$ or $60F = 4.7$, whereby the flow rate $F = 0.08$ cu. cm. per sec. Using equation (15), $(K_m / K_3 E_0)^2 = 0.04$. Using the above values, $E_0 = 2$ mg./liter. Using equation (16), $P = [(7 \times 10^{-6} / 0.01)](1/0.04)$ and, therefore, $P = 0.0175 C_0$.

It can thus be seen that the concentration of the product P is directly proportional to the concentration of glucose in blood. By properly calibrating the detector 91 on the read-out device 92, an indication will be obtained as to the concentration of glucose. Other substances in the blood such as urea, may be measured in a corresponding fashion, by merely hanging the reagent and/or the enzymes associated therewith. For urea, the enzyme would be urease. An entire bank of probes 90, detectors 91, and read-out devices 92 may be provided, each giving an indication of a different substance in the blood. In such case, the reagent would be a composite of the various individual reagents and the requisite enzymes to provide a number of readings respectively indicative of various substances in the blood.

In the above derivation of the formulas used in designing the separating device 100, it was assumed that the flow rates of the reagent and the blood were the same. This is, of course, preferred since the same motor and the motor linkage mechanism can be used to drive the plungers 21 and 31, and the same size syringes 20 and 30 may be utilized. However, the concentration of the selected substance in the blood may still be proportional to the concentration of the product, if the blood analyzer 10 is constructed in such a manner that the flow rates are different. Also, the volumes of the chambers 110 and 110a were assumed to be the same and equal to unity in the above derivation. Again, this operation is preferable since optimum efficiency is achieved. However, the separating device 100 could be designed, and the derivation could be modified, to provide different-sized chambers.

Also, although a specific type driving mechanism was shown and described, it is clear that a variety of mechanisms, may be utilized, the only requisite being that the plungers are moved at a constant velocity into their respective syringes. Also, the probe 90 is one which may be sensitive to ion concentration, color, etc., depending on the specific substance involved.

What has been described, therefore, is a blood analyzer 10 which is small enough and light enough to be portable. It contains all of the needed parts, both to withdraw a sample of blood and to analyze that sample.

It can withdraw the blood and analyze it in less than 3 minutes, preferably within 60 seconds, which is within the time required now for a technician simply to withdraw the blood.

While there has been described what is at present considered to be the preferred embodiment of the present invention, it is to be understood that various changes and modifications can be made therein without departing from the spirit and scope of the invention, and it is intended that all such changes and modifications be covered as fall within the scope of the appended claims.

What is claimed is:

1. A blood analyzer device comprising means for

withdrawing blood from a patient into the device and means for concurrently drawing a supply of reagent into the device, a cavity in the device with inlets and outlets, a semipermeable membrane in the cavity for defining at least two chambers in the cavity, each chamber with an inlet and outlet, the reagent and the blood being coupled in use to respective inlets and being caused to flow through the chambers respectively on opposite sides of the membrane, so that a selected substance in the blood is dialyzed through the membrane to react with the reagent, and means for sensing the amount of said selected substance transferred from

the blood into the reagent as the blood and reagent are caused to flow through the chambers whereby the withdrawing of the blood and the sensing operation are accomplished essentially during the same period of time.

5 2. A device as in claim 1 wherein the axes of the inlet and the outlet of one of said chambers are colinear and the axes of the inlet and the outlet of the other of said chambers are colinear.

10 3. A device as in claim 1 wherein the volumes of said chambers are substantially the same.

4. A device as in claim 1 wherein the flow rates are about 0.17 of the volume of the chamber per second.

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