United States Patent [19]

Kowarski

[11] **3,908,657**

[45] **Sept. 30, 1975**

[54] **SYSTEM FOR CONTINUOUS WITHDRAWAL OF BLOOD**

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[73] Assignee: **The Johns Hopkins University,** Baltimore, Md.

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[52] **U.S. Cl.**..... **128/278;** 128/214 R; 128/214.4; 128/218 A; 128/2 F

[51] **Int. Cl.**[2]..... **A61B 5/00;** A61M 1/00

[58] **Field of Search**..... 128/214 R, 278, 214.4, 128/334 R, 348, 218 A, 2 F, 334; 3/1

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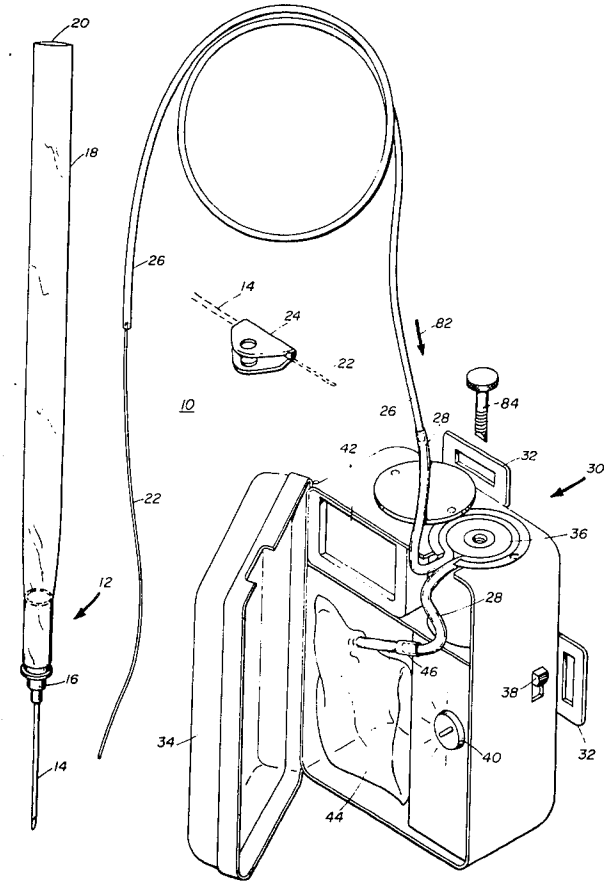
Attorney, Agent, or Firm—Walter G. Finch

[57] **ABSTRACT**

A small, portable, constant withdrawal device is connected to tubing, including a catheter, whose internal walls are coated with heparin. The catheter is inserted intravenously through a disposable needle into a subject such as a human being. The subject may then move about for a selected period when blood is being slowly withdrawn at a prescribed rate and collected in a container within a housing supporting the device. The collected blood may then be analyzed to permit the measurement of the integrated concentration of growth hormone or any substance whose concentration in blood fluctuates widely.

In addition, a portable microdiffusion chamber is incorporated between the indwelling catheter and the extra corporal tubing and is electrically connected through a sensing probe to an associated portable sensory responsive device. This permits analyzation of the extracted blood to determine the in vivo concentration of circulating concentrations of the diffusable fraction of biological materials in the blood.

10 Claims, 7 Drawing Figures



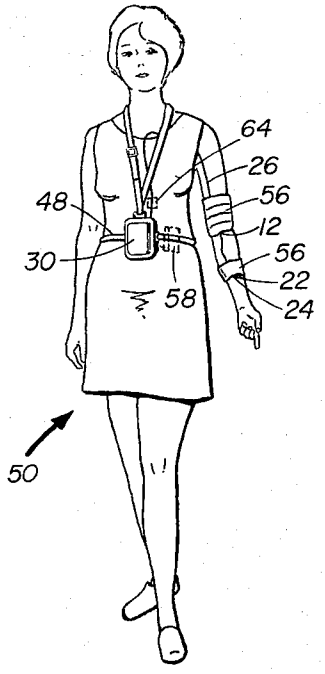

64
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FIG. 2

20
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82
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84
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FIG. 1

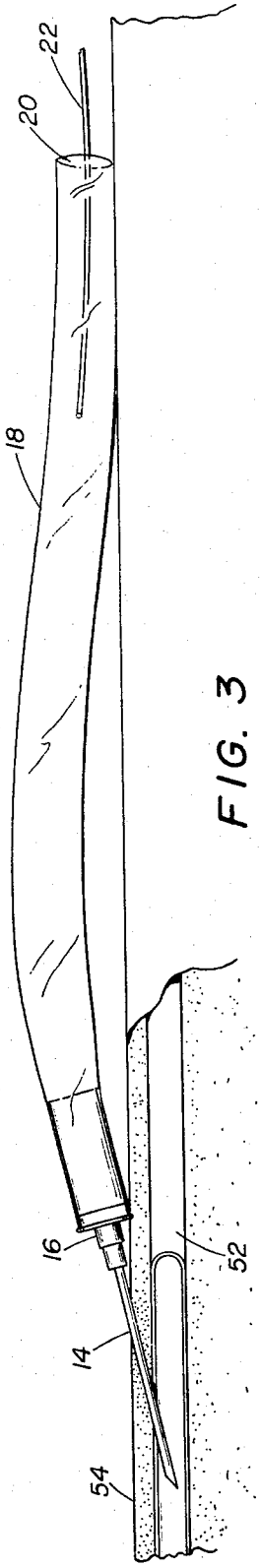

FIG. 3

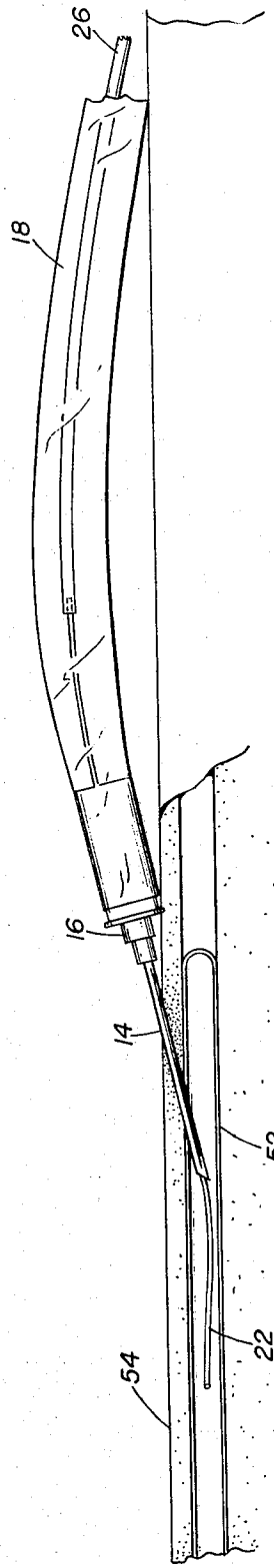

FIG. 4

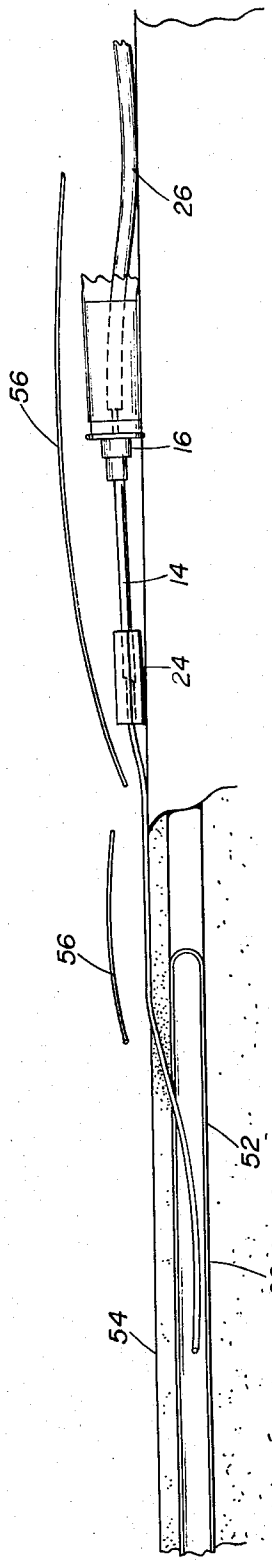

FIG. 5

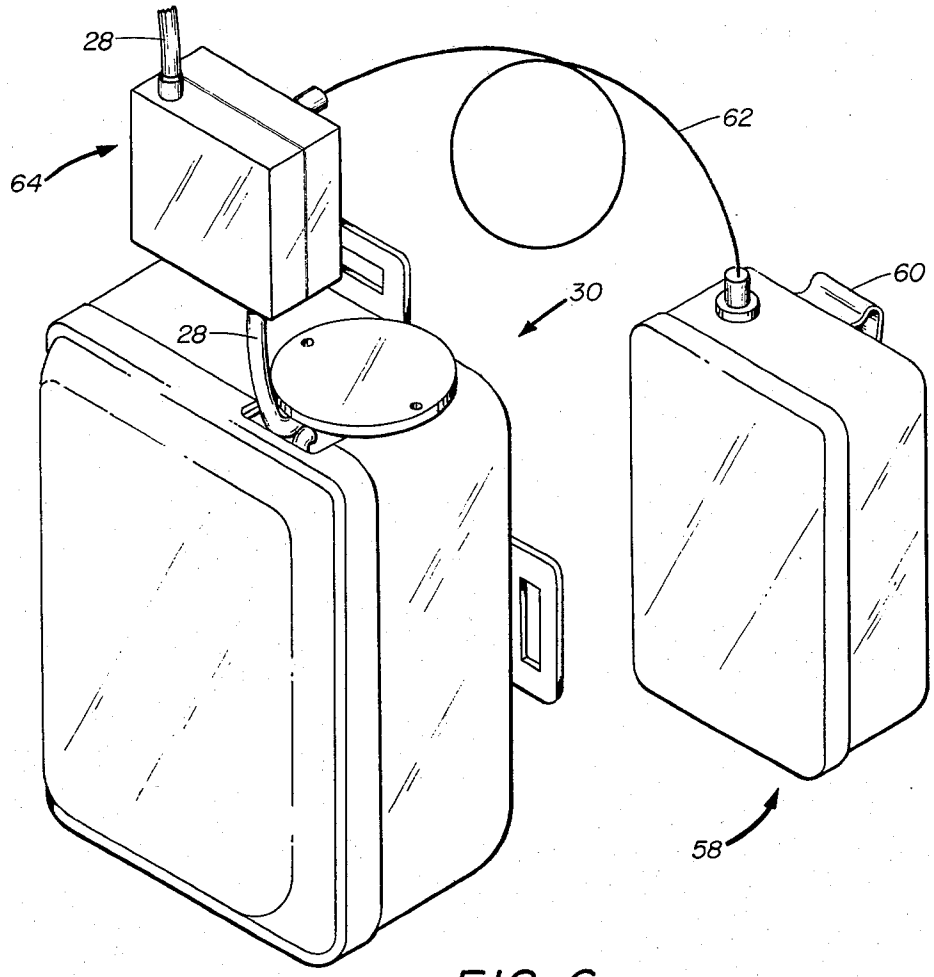

FIG. 6

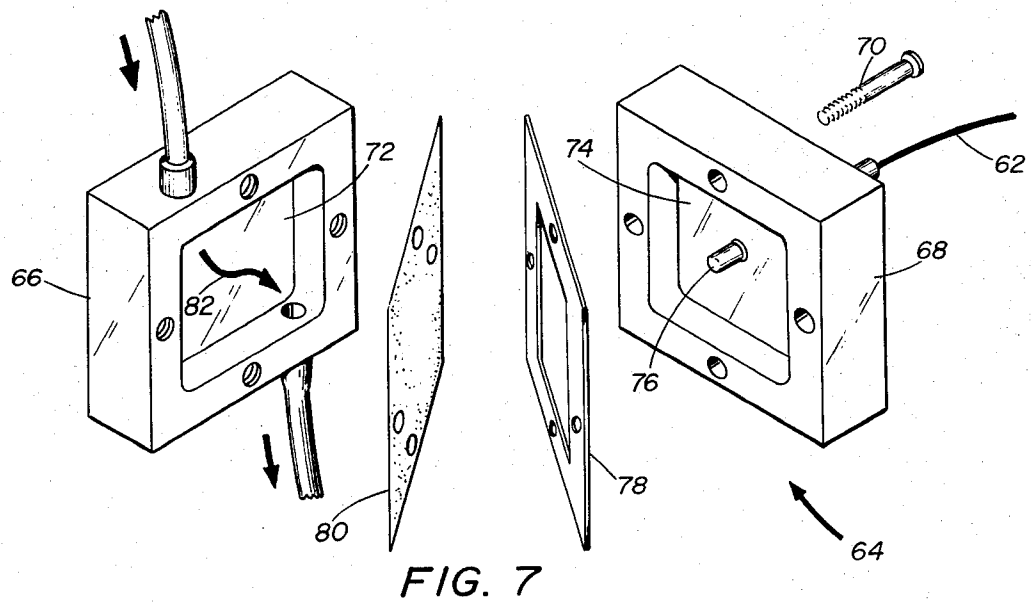

FIG. 7

SYSTEM FOR CONTINUOUS WITHDRAWAL OF BLOOD

This invention relates generally to a system for the continuous withdrawal of blood and more particularly to a system for slowly and continuously drawing and collecting blood from a mobile subject for a selected period.

In order to analyze various properties of constituents contained in the blood, it is necessary that the blood be extracted from the subject. In some instances the blood concentration of a substance changes rapidly and markedly under physiological and pathological conditions. Values obtained from a single, or even multiple, blood specimens drawn in quick succession will not reflect adequately the over-all level of this substance.

For example, the integration of the concentration curves of hormones has been obtained previously by drawing numerous blood samples from a subject, measuring the concentration in each sample, and then calculating the average concentration. Use of this method results in inaccuracies in data collected and calculated as well as resulting in trauma to the subject due to the numerous blood withdrawals.

In an attempt to overcome these disadvantages, complex systems have been developed. For example, in one system, a pump withdraws blood continuously through an indwelling catheter and infuses by still another pump a heparin solution into the withdrawn blood through a smaller catheter inserted into an extra corporal portion of the indwelling catheter to prevent clotting in the extracting system. Obviously the indwelling catheter must be larger than the infusion catheter and, therefore, is limited to indwelling in veins of considerable size. Also two pumps are required. This and other similar systems require intricate arrangements and types of equipment which result in long periods of immobilization of the subject whose blood is being extracted.

Additionally, it is frequently necessary to determine the in vivo concentration of the diffusable fraction of certain biological materials in the blood. If the blood is withdrawn from the subject to measure, for example, the concentration of the diffusible part of any hormone or other material in the blood of the subject, the diffusable fraction frequently changes once the blood is outside of the body. Therefore, intravenous sensing, rather than analyzing of withdrawn blood, is necessary to obtain accurate results.

In many systems where blood is extracted and drawn through various tubes and component parts of an analyzing system, the tubes and parts can be used only for relatively brief periods without clotting of the blood therein. This reduces the opportunity for long range blood withdrawal and the attendant advantages thereof.

It becomes apparent, then, that a need exists for a non-thrombogenic system for extracting blood from a subject over a relatively long period. In addition, there is a need for a non-thrombogenic system for enabling the determination of the in vivo concentration of the diffusable fraction of biological materials in blood. Additionally, there is a need for portability of each of these systems.

It is, therefore, an object of this invention to provide a system for the withdrawing of blood from a subject over an extended, continuous period of time to permit accurate analyzation of the blood.

Another object of this invention is to provide a microdiffusion chamber sensing system for enabling external determination of the in vivo concentration of the diffusable fraction of certain biological materials in the blood.

Still another object of this invention is to provide a non-thrombogenic system which permits the continuous, slow withdrawal of blood through a single catheter over an extended period of time. Another object of this invention is to provide a nonthrombogenic system which will permit the measurement of the integrated concentration of growth hormone or any substance whose concentration in blood fluctuates widely.

Still another object of this invention is to provide a portable system for the continuous withdrawal of blood from a mobile subject.

Other objects and attendant advantages of this invention will become more readily apparent and understood from the following detailed specification and accompanying drawings in which:

FIG. **1** is a pictorial view showing components of a system for withdrawing blood from a subject;

FIG. **2** is a pictorial view showing the system of FIG. **1** attached to a subject;

FIGS. **3, 4** and **5** are pictorial views showing various steps for inserting a catheter of the system of FIG. **1** into the vein of a subject;

FIG. **6** is a pictorial view showing a biological material micro-diffusion and sensing system attached to the system of FIG. **1**; and

FIG. **7** is an exploded pictorial view of the microdiffusion and sensing chamber of the biological material sensing system of FIG. **6.**

Referring now to FIG. **1,** a blood withdrawal system **10** includes a disposable needle assembly **12.** The needle assembly **12** includes a 17 gauge needle **14** mounted in a needle holder **16.** A plastic sleeve **18** is attached at one end thereof to an extension of the needle holder **16.** The other end **20** of the sleeve **18** is open.

The system **10** further includes a 19 gauge catheter **22** composed of a radiopaque material. The catheter **22** is free at one end and is connected to a plastic tube **26** having a larger diameter which, in turn, is connected at its opposite end to another plastic tube **28** having a still larger diameter. The connected sections of the catheter **22** and the tubes **26** and **28** are joined securely by glue.

Thereafter, the internal walls of the catheter **22** and the tubes **26** and **28** are treated to preclude clotting of blood ultimately passing therethrough. This treatment is accomplished in a two step process. Initially, by using a 50/**50** mixture of toluene and petroleum ether, a 5% solution of tridodecylmethylammonium chloride is made. This solution is shaken with 200 milligrams of heparin in 100 milliliters of water. After the emulsion is separated, the supernated portion of this mixture is drawn into the catheter **22** and the tubes **26** and **28** and left in place for two hours. After this, the solution is emptied and filtered air is drawn through the catheter **22** and the tubes **26** and **28** for 24 hours thus drying the solution that impregnated the internal walls of the catheter and the tubes. This is accomplished at room temperature. A solution of 200 milligrams of heparin in 50% methyl alcohol and 50% of water is drawn through the cathter **22** and the tubes **26** and **28** are left for three to 5 hours, withdrawn, and the passageway is air dried by suction as previously described for 12 hours. This

impregnation-coating treatment permits a non-thrombogenic use of the catheter **22** and the tubes **26** and **28** for at least a 24 hour blood withdrawal period.

It is to be noted that great success has been encountered in coating tubes with very narrow internal diameters due to the drying of the wetted internal surfaces with air sucked through them by vacuum rather than the conventional method of vacuum-oven drying.

A housing **30** is formed with strap holders **32** and has a hinged door **34.** The housing **30** contains a rotating milking device **36** which functions as a pump or as a means for controlling the rate of withdrawal of blood from a subject **50** (FIG. **2**). An ON-OFF switch **38** and a timer-control knob **40** are part of a circuit (not shown) which determines when energy from a battery **42** is applied to the milking device **36.** The housing **30** and the various components contained therein are similar to a pump such as a Model ML-5-S available from Sigmamotor, Inc. of Middleport, N.Y. In the Model ML-5-S, the milking device **36** includes a grooved member into which a flexible tube is positioned. An eccentric roller is rotated at a predescribed rate and engages the flexible tube to milk a fluid in the tube therethrough at a prescribed rate. This is normally used to infuse the fluid into the system of a subject.

The housing **30** is formed with a compartment for containing a plastic bag **44** having a tubular port **46.** An intermediate section of the tube **28** is positioned about the grooved member of the milking device **36** within the housing **30** as illustrated in FIG. **1,** and fastened in this position by use of a screw **84.** The remaining end of the tube **28** is inserted into the port **46** to facilitate the eventual collection of withdrawn blood. It should be noted that the plastic bag **44** is only representative of a blood collection facility and could include other facilities such as, for example, test tubes. The eccentric wheel of the milking device **36** can then be rotated at a prescribed rate to withdraw blood from the subject **50.**

Referring to FIG. **2,** straps **48** are used to secure the housing **30** to the subject **50.** The tubes **26** and **28** are positioned through the clothing of the subject **50** so that the catheter **22** is positioned along the inside of one arm of the subject.

Referring to FIGS. **3, 4** and **5,** a peripheral vein **52** in a lower portion of the arm of the subject **50** is selected and the adjacent skin area **54** is sterilized. The needle **14** is then injected into the vein **52** as illustrated in FIG. **3** and the catheter **22** is inserted into the opening **20** of the plastic sleeve **18.**

As illustrated in FIG. **4,** the catheter **22** is then moved through the opening of the needle **14** so that the forward end of the catheter is moved into the vein **52.** As illustrated in FIG. **5,** the needle **14** is withdrawn from the subject **50** and backed over the catheter **22** to the position shown. The removal of the needle **14** is accomplished in such a manner that the forward end of the catheter **22** remains in the vein **52** of the subject **50.**

A plastic clamp **24** (FIGS. **1** and **5**) is clamped about an exposed, intermediate portion of the catheter **22** and placed against the skin of the subject **50.** Adhesive tape **56** is wrapped about the arm of the subject and the clamp **24** as shown in FIG. **2.** The plastic sleeve **18** is then removed from the needle holder **16** and adhesive tape **56** is wrapped about the arm of the subject and the needle **14** and the holder. This permits complete portability of the housing **30** and the contents thereof, the indwelling catheter **22** and tubes **26** and **28.** The subject **50** is free to move about and engage in normal movement.

The milking device **36** is operated by selective positioning of the ON-OFF switch **38** and the timer switch **40.** The timer switch **40** can be set for a selected period of operation of the blood withdrawal system **10.** For example, the system **10** can be controlled to continuously and slowly draw blood from the subject **50** at a constant rate for 24 hours. In addition, the blood can be drawn, for example, at a rate of 1 milliliter per hour.

The internal heparin treatment of the walls of the catheter **22** and the tubes **26** and **28** eliminate any need for heparin infusion into the withdrawn blood and, consequently, for additional pumping and infusion facilities. This enhances the lightweight aspects of the system **10** which include its portability.

The portability of the system **10** permits normal activity, including sleep, for the subject **50** while the blood is being withdrawn from the subject during the blood-withdrawing period. The blood drawn continuously over the extended period of up to 24 hours by use of the system **10** permits analyzation of the blood with more accurate results than are attainable with methods where the subject is immobilized or where there are numerous, separate blood withdrawals.

Referring to FIG. **6,** the system **10** can be modified to include a microdiffusion chamber system **64** located between the indwelling catheter **22** and the milking device **36,** and more specifically in extra-corporal tube **28.** The sensor system **76** is used to sense the concentration of unbound materials in vivo and electrically send a signal over a wire **62** to a recording device **58.** The sensor **62** and the recording device **58** can be, for example, a device available from Space Science Division, of Whittable Corporation, Watham, Mass. The device **58** is contained within a housing which includes a clip **60** to facilitate the attaching of the housing to the waist strap **48** as illustrated in FIG. **2.** This permits portability of the microdiffusion chamber system **64** and associated equipment.

Referring to FIG. **7,** the micodiffusion chamber system **64** includes two plastic housing sections **66** and **68** which are joined together and held by screw fasteners such as fastener **70.** The sections **66** and **68** are formed with chambers **72** and **74,** respectively. A sensor probe **76,** which is connected to the wire **62,** extends into the chamber **74.** A sealing gasket **78** and a silicon cellulose-acetate diffusion membrane **80,** as one example are positioned between the sections **66** and **68** such that the gasket seals the interface of the two sections and the membrane separates the two chambers **72** and **74.** A cellulose-acetate membrane, if desired, can be used instead of the silicon acetate membrane **80.**

Since the withdrawn blood will pass through the chamber **72** as indicated by a direction-of-flow line **82** the diffusable fraction of materials in the blood will diffuse through the membrane **80** into the chamber **74.** The walls of the two chambers must be treated with the two-step process previously described to establish a nonthrombogenic operation.

The probe **76** is the type referred to as a glucose sensor in an article in "Industrial Research" published on September 21, 1972 and appearing on page 27. This probe **76** responds by the generation of electrical energy in relation to the concentration of materials in the blood. Previously, a probe of this type had to be in-

serted intravenously in order to obtain the electrical impulses necessary for measuring the concentrations of materials in the blood.

In use of the microdiffusion system **64** illustrated in FIGS. **6** and **7**, 1 milliliter of Ringer's solution and heparin are contained in the chamber **74**. As blood passes through the chamber **72**, some of the heparin will diffuse through the membrane **80** to render the membrane nonthrombogenic. Also diffusable materials in the blood will diffuse through the membrane **80** into the chamber **74** and will eventually lead to equilibration of the concentration of diffusable materials in the chamber **74** and in venous blood. By use of the probe **76**, detection and measuring of the concentration of such materials in the chamber occurs and permits the measurement of unbound materials in vivo. Thus, the probe **76** need not be inserted intravenously of a subject but can still detect and measure the same properties of the withdrawn blood as if the blood was within the subject. It is also possible to remove the content of chamber **74** and measure directly the concentration of the diffusable materials in it.

In summary, the system **10** permits studies on many aspects of the blood heretofore unattainable due to inaccuracies which result from previous blood collecting processes and vacillations of substances in the blood. For example, an integrated concentration of substances in the blood is that concentration of a substance determined on a specimen which has been collected over an extended period of time and which represents a mean concentration for a specified period of time. A preferable method, both in respect to scientific accuracy and in reducing trauma to the subject, is to determine an integrated concentration by analyzing the concentration of a sample of blood which results from a uniform collection of blood, minute by minute, over an extended period. The use of the system **10** to collect the blood over an extended period, for example 24 hours, permits the practice of the preferable method and thus provided a means of attaining more significant results in blood studies.

A number of hormones and other substances are partially bound to various proteins in blood. The biological activity of these materials is related to the concentration of the unbound moiety rather than to their total concentration. The unbound fraction in vitro is determinable by measuring the diffusion fraction. Results obtained by such in vitro methods are of limited usefulness since the studies are conducted outside the body. Also, significant changes in the equilibrium between bound and free fractions occur because of pH changes and other in vitro changes that often are unavoidable. The errors in measuring free concentrations of hormones in vitro may explain a number of inconsistencies between the concentration of the unbound biological materials, measured by presently available methods, and their known biological activity.

The development of the small catheter **22**, which will permit the measurements of integrated concentrations of substances, and the development of the small, nonthrombogenic, diffusion chamber system **64**, which can be inserted between the catheter **22** and the extracorporal tube **28**, will permit the determination of production rates of various substances which have not previously been determinable and a true, free fraction of the substance under study. The latter is possible because one can expect an equilibrium will be established between the diffusable fraction of materials in blood and the Ringer's solution contained in the chamber **74**. In this type of study where the blood would constantly come from a vein, the results obtained for the free fraction will better reflect conditions inside the body and give more accurate data regarding interrelationship of hormones and other substances than can currently be determined using crude in vitro techniques.

It is possible to use parts of the INFUSOR SET made by Sorenson Research Company of Salt Lake City, Utah, instead of parts **14, 16, 18,** and **22** described in FIG. **1**.

Obviously many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims the invention may be practiced otherwise than as specifically described.

What is claimed is:

1. A system for continuously withdrawing blood from a subject comprising, means having openings only at opposite ends thereof insertable at one end thereof into a vein of the subject for providing a nonthrombogenic passageway for blood being withdrawn from the subject, said passageway having its inner surfaces permanently coated with an anti-coagulent substance to preclude clotting of the blood being withdrawn through said means and thereby render the system nonthrombogenic in operation, means externally of the subject and connected to the other end of said nonthrombogenic passageway-providing means for collecting the withdrawn blood, and means engaging only an extracorporal intermediate section of said nonthrombogenic passageway-providing means for controlling the continuous withdrawing of the blood slowly from the vein at a predetermined constant rate and for a predetermined extended period during which the insertable means is in the vein of the subject.

2. A system for continuously withdrawing blood as recited in claim **1** wherein the vein-insertable end of said passageway-providing means is a catheter of a predetermined gauge size.

3. A system for continuously withdrawing blood as recited in claim **1**, wherein said anti-coagulent substance is heparin bound to the inner surfaces of said passageway that come in contact with blood.

4. A system for continuously withdrawing blood as recited in claim **1**, wherein said withdrawing means includes a milking device having a rotating eccentric member which engages an external section of the passageway-providing means and continuously controls the rate of passage of blood through said passageway-providing means.

5. A system for continuously withdrawing blood as recited in claim **1**, wherein said controlling means controls the rate at which blood is withdrawn such that the rate is constant.

6. A system for continuously withdrawing blood as recited in claim **1**, wherein said controlling means controls the withdrawal of blood through the nonthrombogenic passageway-providing means for the predetermined extended period of up to at least twenty-four hours.

7. A system for continuously withdrawing blood as recited in claim **1**, wherein said system is sufficiently light in weight and compact in size and further comprises means for attaching the system entirely to the subject to permit portability of said system and free-

dom of mobility of the subject while the blood is being withdrawn.

8. A system for continuously withdrawing blood as recited in claim **1**, and additionally means having a rigid passageway with openings at opposite ends thereof and insertable into the vein of the subject with one open end located within the vein and the other open end located externally of the subject for providing a rigid guide to facilitate the insertion of the one end of the nonthrombogenic passageway-providing means into the vein.

9. A system for continuously withdrawing blood as recited in claim **8**, and additionally means for permitting withdrawal of the guide-providing means from the vein of the subject while the one end of the nonthrombogenic passageway-providing means remains within the vein to facilitate withdrawing of the blood.

10. A system for continuously withdrawing blood as recited in claim **8**, wherein the guide-providing means includes a needle having a passageway with openings at opposite ends thereof and being of sufficient diameter to permit free relative movement of the nonthrombogenic passageway-providing means therethrough.

* * * * *

Disclaimer

3,908,657.—*Avinoam Kowarski*, Baltimore, Md. SYSTEM FOR CONTINUOUS WITHDRAWAL OF BLOOD. Patent dated Sept. 30, 1975. Disclaimer filed July 5, 1977, by the assignee, *The Johns Hopkins University*.

Hereby enters this disclaimer to all claims of said patent.

[*Official Gazette August 23, 1977.*]