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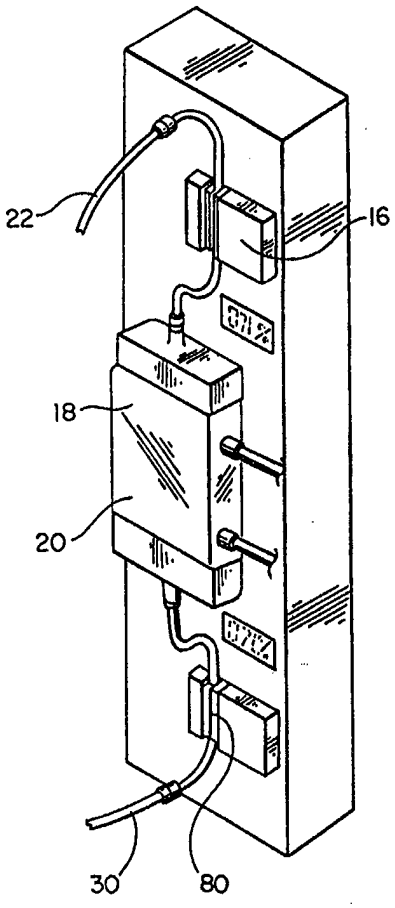
(54) Title: DIALYSIS MONITORING METHOD AND APPARATUS

(57) Abstract

This invention is a non–invasive, real time dialysis monitor for monitoring the process of dialysis. Uremic toxin as well as other blood parameter levels are measured (16, 80), and the measured constituents are used to monitor the progress of dialysis treatments (18, 20). The parameters can be optically monitored and determined by spectro–analysis.



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DIALYSIS MONITORING METHOD AND APPARATUS

Related Cases

This application claims the benefit of U.S. Provisional Application No. 60/030,113, filed November 1, 1996.

Background of the Invention

The present invention pertains to a hemodialysis monitoring method and apparatus. In a preferred embodiment, the monitoring method and device can be used to assess the adequacy of hemodialysis treatment.

In clinical settings, it is generally desired to ensure the adequacy of the treatment and to optimize the length of time a patient must be dialyzed. During the dialysis session, toxins are eliminated from the patient's blood. The identity of all of the toxins which may adversely effect the quality of life and life expectancy are not known, however, those toxins found in urine are believed to be significant. These toxins include urea, creatinine and others.

The equation:

$$Kt/V \geq 1.2$$

has been used to estimate the adequacy of dialysis. K is the urea clearance of a particular dialyzer measured in milliliters of blood cleared of urea per minute. The t is the dialysis treatment time in minutes, and V reflects

the volume of distribution of urea which is generally approximately equal to total body fluid volume.

K is a function of the particular filter used in the dialyzer and blood flow rate. V is generally estimated for each individual based upon the patient's height, weight, sex and the like. Given K and V, the formula can be solved for t, the lowest value of t satisfying the formula being the minimum desirable dialysis treatment time.

It can be appreciated that there are various limitations to the adequacy of this formulation. For example, since K is estimated for a given filter product at a particular flow rate, re-use of the filter or variability in the manufacture of the filter can effect the value of K. V also has an approximate value. Consequently, the estimated time t is effected by these inaccuracies.

Kt/V is defined as a function of uremic toxin concentrations observed at the beginning and at time t during dialysis.

$$Kt/V = \ln (C_o/C_t)$$

Where C_o is the uremic toxin concentration at the beginning of the treatment, and C_t is at time t.

Summary of the Invention

Applicant has devised a non-invasive, on-line, real-time dialysis monitor which can monitor the progress of dialysis via monitoring the concentration of uremic toxin. In a preferred embodiment, on the blood side of the dialyzer, the uremic toxins concentration of urea and creatinine, besides the clinically important bicarbonate, hematocrit, total protein and albumin can be optically monitored as well as pH. On the dialysate side of the dialyzer, the concentration of urea, creatinine and total protein can be optically monitored as well as similar parameters can be monitored optically in the serum ultrafiltrate, on certain hemodialyzers having separate ultrafiltration means.

From these measurements, a concentration profile can be developed during and after dialysis to determine Kt/V, 2-pool Kt/V and by measuring or estimating the ultrafiltration, the volume corrected Kt/V for a particular patient and treatment. By monitoring the concentration profile of urea during and after dialysis, the urea "re-bound" effect can be taken into account. Re-bound is caused by the non-uniform distribution of urea and other solutes among various body compartments that develops during dialysis and causes reduced solute removal.

Brief Description of the Drawings

Figure 1 is a schematic view of a dialysis monitoring device corresponding to the present invention;

Figure 2 is a view of an optical sensor in accordance with the present invention;

Figure 3 is an alternate embodiment of an optical sensor in accordance with the present invention;

Figure 4 is a view of the optical sensor of Figure 3 in combination with the control circuitry;

Figure 5 is a view of a calibration mechanism for the optical sensor;

Figure 6 is an infrared spectral plot of a set of blood samples;

Figure 7 is a plot of results of a test using a sensor in accordance with the present invention;

Figure 8 is yet another plot of results of a test using a sensor in accordance with the present invention;

Figure 9 is yet another plot of results of a test using a sensor in accordance with the present invention;

Figure 10 is yet another plot of results of a test using a sensor in accordance with the present invention;

Figure 11 is a chart showing a sample set of adequacy parameters which can be derived based upon the readings obtained from the optical sensors of the device of the present invention;

Figure 12 is a quasi-schematic drawing of yet another embodiment of the dialysis monitoring device in accordance with the present invention;

Figure 13 is a schematic drawing of the apparatus of Figure 12;

Figure 14 is a schematic drawing of the apparatus of Figure 12 showing the location of the parameter measurements;

Figure 15 is yet another schematic drawing of the apparatus of Figure 12 showing the location of parameter measurements;

Figure 16a is a plot of urea toxins versus dialysis time;

Figure 16b is a plot of Q_B versus dialysis time; and

Figure 16c is a plot of UR versus dialysis time.

Detailed Description of the Preferred Embodiments

Figure 1 is a schematic view of the preferred embodiment of a dialysis monitoring device 10 of the present invention. Sensor 12 (S1) optically monitors ultrafiltrate on-line and in real-time during dialysis. A second sensor 14 (S2) likewise monitors dialysate on-line, optically in real-time during dialysis. Sensor 16 (S3) monitors arterial access blood, on-line, optically and in real-time. One or more of these sensors may not be required in a particular application depending upon

the particular blood or dialysate side parameters to be monitored. The sensors preferably operate in the near-infrared.

Dialysis monitoring device 10 also includes an ultrafilter 18 and hemodialyzer. These components as well as the sensors are linked together in a system such that material access blood flows from a patient A through sensor 16 and then into ultrafilter 18. Ultrafiltrate is diverted from ultrafilter 18 through line 24 through monitor 12. Blood then passes through line 26 from ultrafilter 18 to hemodialyzer 20. From hemodialyzer 20 dialysate is diverted through sensor 14 by line 28. Dialyzer 20 includes a counter current water input line 27. Venous access blood is then returned to patient A through line 30.

Figure 2 shows an optical sensor of the preferred embodiment of the present invention including a light source 32, collimating optics 34, optical modulator 36, filter 38, focusing optics 40, fluid flow through cell 42, reimaging optics 44, detector 46. The blood, dialysate or ultrafiltrate can pass through inlet port 48 and exit through outlet port 50.

Figure 3 shows an alternate embodiment of the sensor of Figure 2 which does not include the reimaging optics 44. In this arrangement, the detector is placed in close proximity to the flow cell, containing the blood. The

light scattered by the blood cells in all direction can be efficiently collected by a larger area detector in such an arrangement. U.S. Patent Application Serial No. 08/512,940 entitled "METHOD FOR NON-INVASIVE BLOOD ANALYTE MEASUREMENT WITH IMPROVED OPTICAL INTERFACE", filed August 9, 1995 is incorporated herein by reference.

Figure 4 shows the sensor of Figure 3 coupled to a controller 52 which is interconnected with optical modulator 36 to control the frequency of the light projected into the fluid flow through cell 42. Controller 52 also processes the signals from detector 46 caused by incident light emanating from fluid flow through cell 6. These signals are processed through a detector pre-amplifier 56 and analog to a digital converter 54 prior to being received and processed by controller 52.

In order to ensure that the optical monitor stays calibrated, it is advantageous to measure a sample of known concentration periodically. This sample should preferably be in a similar sample cell to the monitoring cell and have similar optical characteristics to the fluid to be measured. In one preferred embodiment, the reference cell 58 is moved automatically into the beam as shown in Figure 5, everytime the sample cell 42 is removed. The optical illuminate 60 and detector 46 stay in place while the guide mechanism 62 positions reference

cell 58, energized by spring 64. Calibration of the instrument is ongoing while the reference is in the beam.

Figure 6 shows a typical set of near-infrared spectra of a set of blood samples containing different amounts of urea, creatinine, total protein and hematocrit. As it is obvious from the spectra, the materials with the different concentrations show very similar absorbance spectral shapes.

Multiple least squares (MLS) or partial least squares algorithms can be used to correlate the known concentrations with the observed spectrum. The sample or samples excluded from this calibration procedure serve to verify the performance of the calibration. This so called prediction is characterized by the correlation coefficient (R) and the standard error of prediction (SEP). When a predetermined number of samples are left out of the calibration, and used for prediction in a systematic fashion, such that all points are left out at least once, the performance of such a composite prediction is characterized by the cross validated standard error of prediction (CV-SEP).

Figure 7 shows the results of a test using a sensor in accordance with the present invention comparing the known urea concentration in mg/dl of a sample with that obtained by the optical sensor. Figures 8, 9 and 10 show

the same relationship for creatinine (mg/dl), glucose (mg/dl) and hematocrit (%), respectively.

Figure 11 shows a sample set of adequacy parameters which can be derived based upon the readings obtained from the optical sensors. Measurements of uremic toxin concentration can be used to calculate single pool Kt/V (spKt/V) and URR 66, effective Kt/V, for the estimation of (eKt/V) and URR 68. Measurement of the re-bound effect 70 which in turn allows estimation of V 72 and thus the 2-pool Kt/V (dpKt/V) and URR 74.

In the preferred embodiment, the monitor is connected to the hemodialyzer via its serial port. The monitor can read all of the relevant dialyzer settings remotely at all times. Among other parameters, the blood flow in the dialyzer (Q_B), the ultrafiltration target (UF) and the actual ultrafiltration rate (UF(t)) can be thus acquired. These values can be used to calculate ultrafiltration corrected Kt/V and URR 76 can also be calculated.

The near-infrared measurement of the spectrum of the blood allows the precise measurement of the red blood cell concentration. The red blood cells (RBC's) are generated relatively slowly in the body, so a change in the concentration of the RBC's is an indication of the blood volume change. As opposed to the visible colorimetric method, in the near-infrared, the overtones

and combination bands of the hemoglobin itself are manifested and detected not just the change of color. The hematocrit level can be used to calculate blood volume change and, in turn, the corrected Kt/V (spKt/V, dpKt/V and eKt/V) and URR 78 can be calculated. All of these calculations can be made by a microprocessor or the like interconnected with the sensor controllers.

In yet another preferred embodiment of the present invention, an optical sensor 80 as described above, is placed on the "venous" side of the dialyzer. This optical sensor can monitor the blood returning from the dialyzer to the patient, as shown in Figure 12. By providing sensors on both the arterial and venous side of the dialyzer, measurement of the Recirculation on-line is possible without saline bolus, cooling the blood or any other manipulation. From the Recirculation can be calculated the vascular access blood flow as well as other clinically relevant parameters. Figure 13 is a schematic of the device shown in Figure 12 including a parastolic pump 81.

Figures 14-16 show how several clinically relevant parameters can be calculated based upon the sensor readings. As described above with respect to the previous embodiment, the venous side sensor can also be connected to a microprocessor for real-time calculation of these parameters. In addition, the venous side sensor

could be added to the embodiment shown in Figure 1 to provide the monitoring and calculation abilities of both that embodiment and the one shown in Figure 12.

Figure 14 shows a determination of the Recirculation R, where Q_B is greater than Q_A.

$$R = \frac{Shunt\ Flow}{Blood\ Flow} = \frac{Q_B - Q_A}{Q_B}$$

Substituting for measured concentrate terms yields.

$$R = \frac{C_S - C_A}{C_S - C_V}$$

In this case, vascular access flow Q_A can be calculated as follows:

$$Q_A = Q_B\left(1 - \frac{(C_S - C_A)}{(C_S - C_V)}\right)$$

In yet another case as shown in Figure 15, were Q_A is greater than Q_B vascular access flow can be calculated as follows:

$$Q_A = Q_B \frac{(C_A - C_V)}{(C_S - C_A)}$$

As shown previously, recirculation can be calculated directly from measurements of systemic concentration

(C_S), arterial concentration (C_A), and venous concentration (C_V). Additionally, recirculation can be estimated by varying the dialyzer pump speed (Q_B) then recirculation occurs and the urea removal rate is reduced due to the presence of recirculation. If no recirculation is present, the urea removal rate will increase due to increased flow through the dialyzer. These characteristic changes can be used to determine the presence and amount of recirculation. In practice, recirculation measurements are made by obtaining systemic, arterial, and venous blood samples. This process typically requires that the dialysis session be stopped momentarily to obtain the above blood samples, and represents a single point in time measurement. By modulating the pump speed in a pre-determined fashion over the course of the dialysis session, the presence of recirculation and the amount of recirculation can be calculated at multiple points in time without interruption of the dialysis session. The calculation or estimation of recirculation requires the use of measured arterial (C_A) and venous concentrations (C_V) in combination with the dialyzer parameters, including pump speed (Q_B).

Figure 16a shows the typical relationship between arterial and venous concentration levels as a function of increasing dialysis time. In Figure 16b, the pump speed

to the dialyzer and subsequent flow through the dialyzer is changed. Three different levels are shown. In Figure 16c, the influence of these changes can be seen on the urea removal rate.

Numerous characteristics and advantages of the invention covered by this document have been set forth in the foregoing description. It will be understood, however, that this disclosure is, in many respects, only illustrative. Changes may be made in details, particularly in matters of shape, size, and arrangement of parts without exceeding the scope of the invention. The inventions's scope is, of course, defined in the language in which the appended claims are expressed.

What is claimed is:

1. Method of measuring urea or creatinine or total protein or glucose in whole blood non-invasively, comprising the steps of:

using light transmitted through or reflected from a portion of the whole blood contained or held by transparent optical elements such as a window or other cuvette means to spectrographically determine the blood characteristics used to calculate the measurement.

2. Method of claim 1, wherein said light is near-infrared with a wavelength between 1 um to 2.5 um (10000 to 4000 cm-1).

3. Method of claim 1, wherein the said whole blood is intermittently or continuously moved through said cuvette means.

4. Method of claim 2, wherein said whole blood is intermittently or continuously moved through said cuvette means.

5. Method of measuring urea or creatinine or total protein or albumin or glucose non-invasively comprising the step of using near-infrared light in dialysate.

6. Method of measuring urea or creatinine or total protein or albumin or glucose non-invasively comprising the step of using near-infrared light in ultrafiltrate.

7. Method of non-invasively measuring adequacy of hemodialysis parameters spKt/V during dialysis, without drawing a sample of blood from the patient or from the hemodialysis bloodlines, comprising the steps of:

shining near-infrared light characteristics to the uremic toxins urea or creatinine through a portion or whole stream of the extracorpeal blood circuit and detecting the light intensity change characteristics to said uremic toxins;

calculating the concentrations at the beginning and at the end of the hemodialysis treatment from said characteristic light intensity changes; and

calculating the spKt/V as ln (urea concentration at the beginning of the treatment/urea concentration at the end of the treatment).

8. Method of claim 7, wherein the expected weight loss or actual change of weight of the patient during treatment due to ultrafiltration is used in combination with the non-invasively measured uremic toxin or to estimate the corrected spKt/V, eKt/V, URR or dpKt/V.

9. Method of claim 7, wherein the Hcrit or the blood volume change during treatment due to ultrafiltration is used in combination with the non-invasively measured uremic toxin or to estimate the corrected spKt/V, eKt/V, URR, or dpKt/V.

10. Method of claim 7, wherein the Hcrit or the blood volume change during treatment due to ultrafiltration is used in combination with the expected weight loss or actual change of weight of the patient during treatment due to ultrafiltration and the non-invasively measured uremic toxin or to estimate the corrected spKt/V, eKt/V, URR or dpKt/V.

11. Method of non-invasively measuring adequacy of hemodialysis parameter, eKt/V, during dialysis, without drawing a sample of blood from the patient or from the hemodialysis bloodlines, comprising the steps of:

shining near-infrared light characteristics to the uremic toxins urea or creatinine through a portion or whole stream of the extracorpeal blood circuit and detecting the light intensity change characteristics of said uremic toxins;

calculating the concentrations at the beginning and during hemodialysis treatment from said characteristic light intensity changes;

calculating the concentrations 30 minutes to 1 hour following the hemodialysis treatment from said characteristic light intensity changes or predicting the urea concentration after the urea rebound using urea concentration data taken during the hemodialysis; and

calculating eKt/V from ln (urea concentration at the beginning of the treatment/urea concentration measured at or estimated 30 minutes to 1 hour after the end of the hemodialysis treatment).

12. Method of non-invasively measuring adequacy of hemodialysis parameter URR during dialysis without drawing a sample of blood from the patient or from the hemodialysis bloodlines, comprising the steps of:

shining near-infrared light characteristic to the uremic toxins urea or creatinine through a portion or whole stream of the extracorpeal blood circuit and detecting the light intensity change characteristic to said uremic toxins;

calculating the concentrations at the beginning and at the end of the hemodialysis treatment from said characteristic light intensity changes; and

calculating the URR as 1-(urea concentration at the beginning of the treatment/urea concentration at the end of the treatment).

13. Method of non-invasively measuring a plurality of concentrations of the uremic toxins of urea or creatinine during the hemodialysis and calculating (estimating) the hemodialysis adequacy parameters, spKt/V, eKt/V, URR comprising the step of using least squares fit of said adequacy parameters to the plurality of concentration parameters.

14. Method of non-invasively measuring a plurality of concentrations of the uremic toxins of urea or creatinine during the hemodialysis and calculating (estimating) the best fit of the 2-pool kinetic curve to the observed uremic toxin concentration curve comprising the step of using least squares fit of the 2-pool kinetic adequacy parameter dpKt/V to the plurality of concentration parameters.

15. Apparatus for the measurement of uremic toxins, urea or creatinine comprising:

a near-infrared light source;

means to direct light from the near-infrared light source onto whole blood;

means to contain whole blood such that said near-infrared light can be transmitted through or reflected from the whole blood;

means to select or modulate different wavelengths of said near-infrared radiation;

means to detect near-infrared radiation;

signal processing and/or computing means to calculate the concentration of said uremic toxins.

16. Apparatus of claim 15, wherein said means to select or modulate near-infrared radiation is an interferometer.

17. Apparatus of claim 15, wherein said near-infrared radiation is restricted to 4000 to 5000 cm-1 and/or to 5000 to 8000 cm-1 (final numbers to be determined).

18. Apparatus of claim 17, wherein the short wavelength side of the wavelength range 4000 to 5000 cm-1 is restricted by the use of a germanium filter.

19. Apparatus of claim 15, wherein said means to contain whole blood is made of a biocompatible and near-infrared transparent material, such as polysulfone, polymethylmetacrylate, transparent polytetrafluoroethylene (Teflon), ABS or glass.

20. Apparatus of claim 15, characterized by having an additional built-in referencing means having similar optical characteristics to the transparent fluid cell containing whole blood dialysate or ultrafiltrate utilized to measure said fluids.

21. Apparatus of claim 15, characterized by a mechanism that automatically moves the said reference material into the near-infrared beam, upon removal of the blood containing optical cell.

22. Method of estimating the time required to achieve adequate hemodialysis comprising the steps of continuously measuring the actual adequacy parameter spKt/V or eKt/V or dpKt/V or URR; and predicting the time when a prescribed target value of said adequacy parameter will be reached.

23. Method of monitoring hemodialysis comprising the steps of having two non-invasive optical detection means in the hemodialysis blood circuit, one in the arterial side and one in the venous side of the dialyzer cartridge.

24. Method of measuring recirculation in hemodialysis comprising the steps of:

non-invasively measuring the arterial side uremic toxin, urea, or creatinine concentration during hemodialysis (Ca);

non-invasively measuring the venous side uremic toxin concentration (Cv);

slowing down the dialysis pump to minimize recirculation;

non-invasively measuring the systemic uremic toxin concentration on the arterial side (Cs); and

calculating recirculation from Cs, Ca and Cv using the equation:

$$R = (Cs-Ca)/(Cs-Cv).$$

25. Method of claim 24, wherein the non-invasive method of determining the concentration of said uremic toxins is near-infrared spectroscopy.

26. Method of claim 25, wherein said near-infrared spectroscopy is carried out in the 4200 to 4800 cm-1 wavelength region.

27. Apparatus to measure recirculation during hemodialysis comprising:

a near-infrared light source;

means to direct light from the near-infrared light source onto whole blood on the arterial side of the dialyzer in the blood circuit;

means to direct light from the near-infrared light source onto whole blood on the venous side of the dialyzer in the blood circuit;

means to contain whole blood such that said near-infrared light can be transmitted through or reflected from the whole blood such on the arterial side of the dialyzer in the blood circuit;

means to contain whole blood such that said near-infrared light can be transmitted through or reflected from the whole blood on the venous side of the dialyzer in the blood circuit;

means to select or modulate different wavelengths of said near-infrared radiation, means to detect near-infrared radiation;

signal processing and/or computing means to calculate the concentration of said uremic toxins in both the arterial and venous side of the dialyzer from the detected characteristic light intensity changes.

28. Apparatus of claim 27, wherein said means to select or modulate near-infrared radiation is an interferometer.

29. Apparatus of claim 27, wherein said near-infrared radiation is restricted to 4000 to 5000 cm-1 and/or to 5000 to 8000 cm-1.

30. Apparatus of claim 27, wherein the short wavelength of the wavelength range is restricted by the use of a germanium filter.

31. Apparatus of claim 27, wherein said means to contain whole blood is made of a biocompatible and near-infrared transparent material, such as polysulfone, polymethylmetacrylate, transparent polytetrafluoroethylene (Teflon), ABS or glass.

32. Apparatus of claim 27, having an additional built-in referencing means having similar optical characteristics to the transparent fluid cell utilized to measure whole blood on either the arterial or the venous side of the dialyzer.

33. Apparatus of claim 27, including means for moving said reference material into the near-infrared beam, upon removal of the blood containing optical cell.

34. Method of measuring vascular access flow in the presence of access recirculation by non-invasively comprising the steps of:

measuring the arterial side uremic toxin, urea or creatinine concentration during hemodialysis (Ca);

non-invasively measuring the venous side uremic toxin concentration (Cv);

slowing down the dialysis pump to minimize recirculation;

non-invasively measuring the systemic uremic toxin concentration (Cs); and

calculating vascular access flow from Cs, Ca, Cv, and the dialyzer flow (QB) using:

$$QA = QB\ (1-(Cs-Ca)\ /\ (Cs-Cv)).$$

35. Method of measuring vascular access flow in the case of negligible or no recirculation comprising the steps of:

slowing down the dialysis pump to minimize recirculation;

non-invasively measuring the systemic uremic toxin concentration (Cs);

switching the arterial and venous access lines of the dialysis blood circuit;

non-invasively measuring the arterial side uremic toxin, urea or creatinine concentration during hemodialysis (Ca);

non-invasively measuring the venous side uremic toxin concentration (Cv); and

calculating vascular access flow from Cs, Ca, Cv, and the dialyzer flow (QB) using:

$$QA = QB\ (Ca-Cv)\ /\ (Cs-Ca).$$

36. Method of estimating vascular access flow from a plurality of recirculation measurements at different dialyzer blood flow rates (QB), comprising the step of calculating vascular access flow from said recirculation data and using graphical or statistical means to extrapolate the vascular access flow to zero dialyzer blood flow rate.

37. Method of measuring total uremic toxin removal rate by non-invasively monitoring said uremic toxin concentration in the blood both before and after the dialyzer cartridge, comprising the step of measuring the dialyzer flow rate at the same time and measuring or estimating the ultrafiltration rate:

$$Rate\ of\ uremic\ toxin\ removal\ rate, UR = QB(Ca-Cv) + \frac{UF}{t_d}C_v$$

38. Method of measuring the total amount of uremic toxin removed during hemodialysis comprising the step of integrating the removal rate of said uremic toxin as measured according to claim 39 over the duration of the hemodialysis:

$$\sum UR = \int_0^{t_d} UR(t)\,dt$$

39. Method of measuring the volume of uremic toxin distribution by measuring the total removed uremic toxin according to claim 38, further comprising the step of measuring the concentration of said uremic toxins at the beginning and at the end of hemodialysis:

$$V = \frac{\Sigma UR}{C_0 - C_t}$$

Fig.1

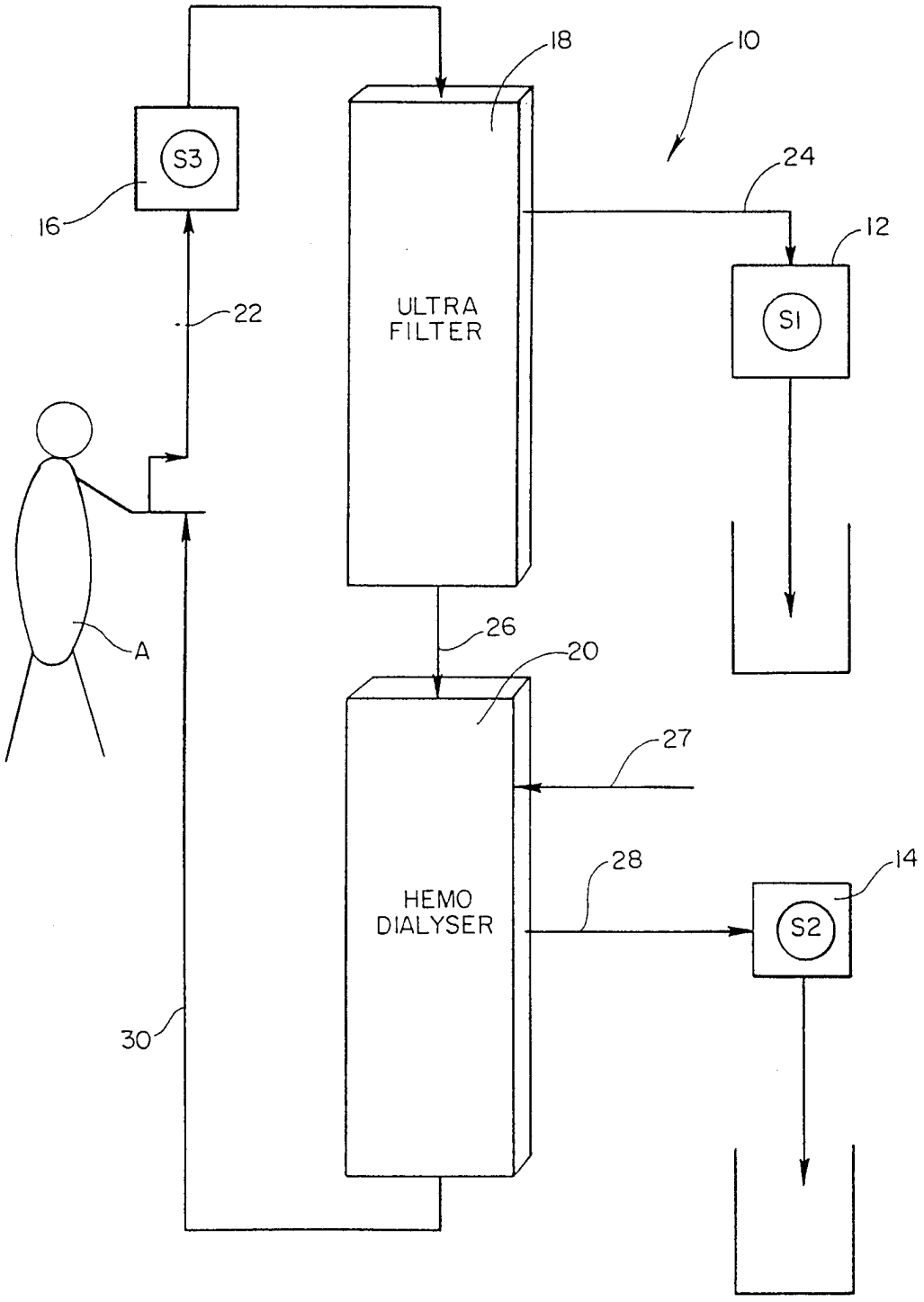
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Fig.2

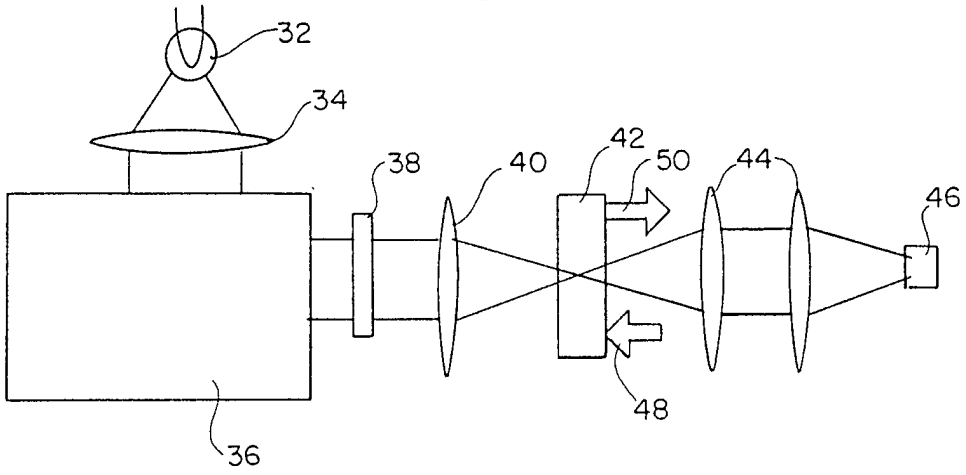


Fig.3

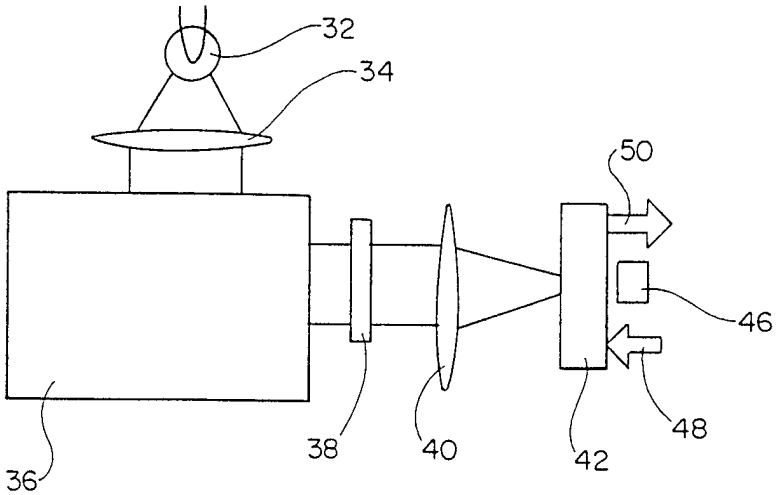


Fig.4

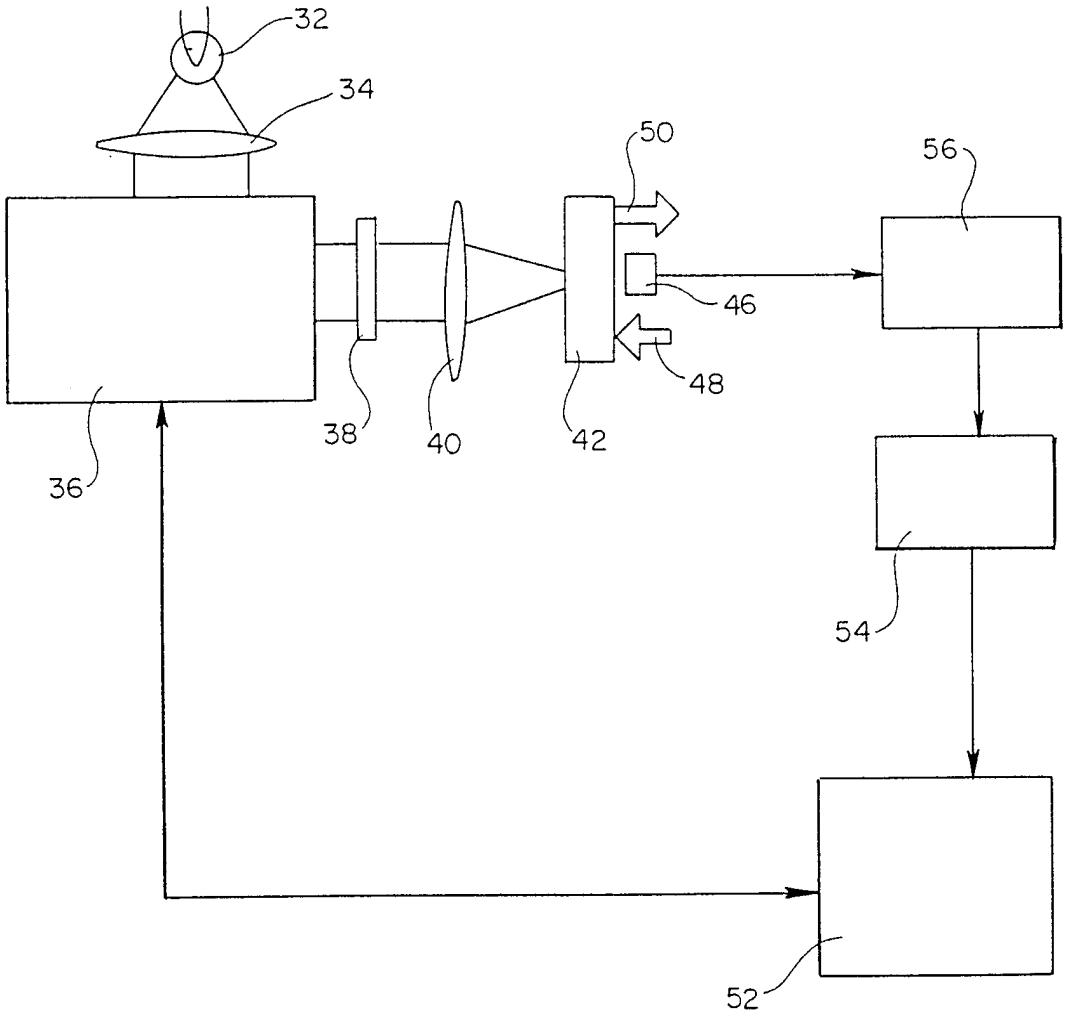


Fig.5

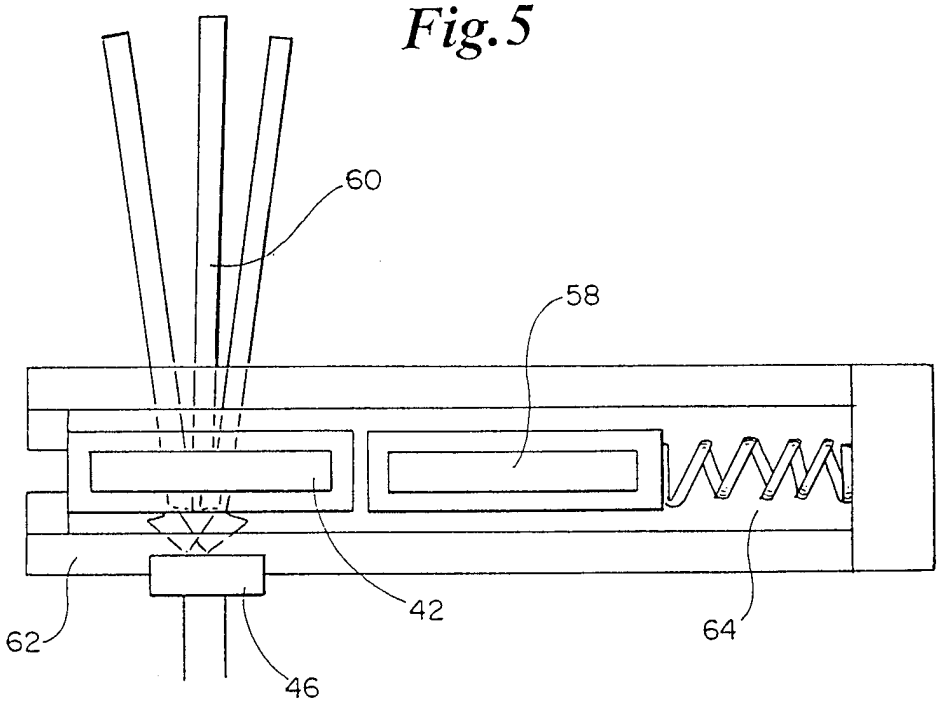


Fig.6

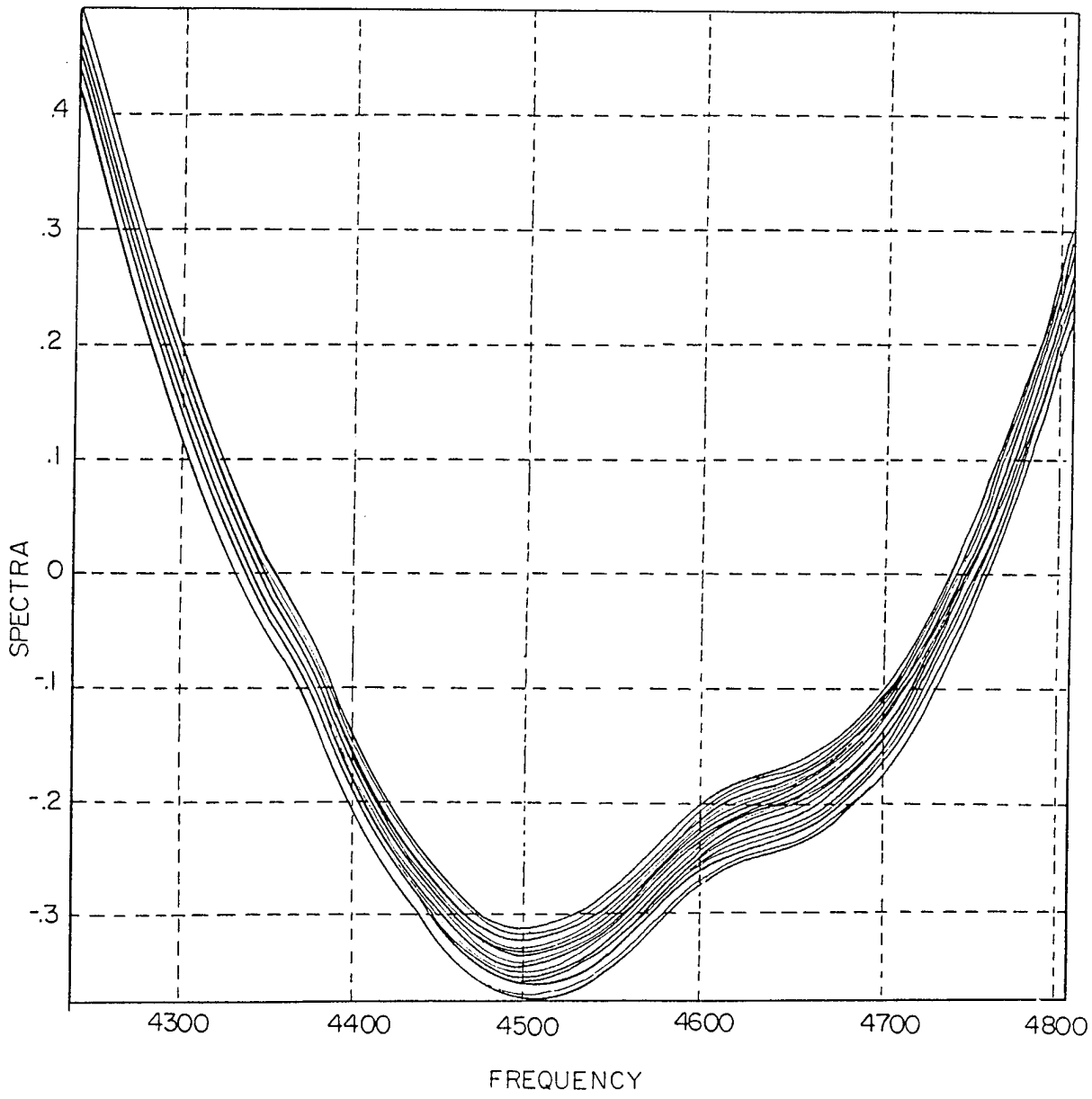


Fig. 7

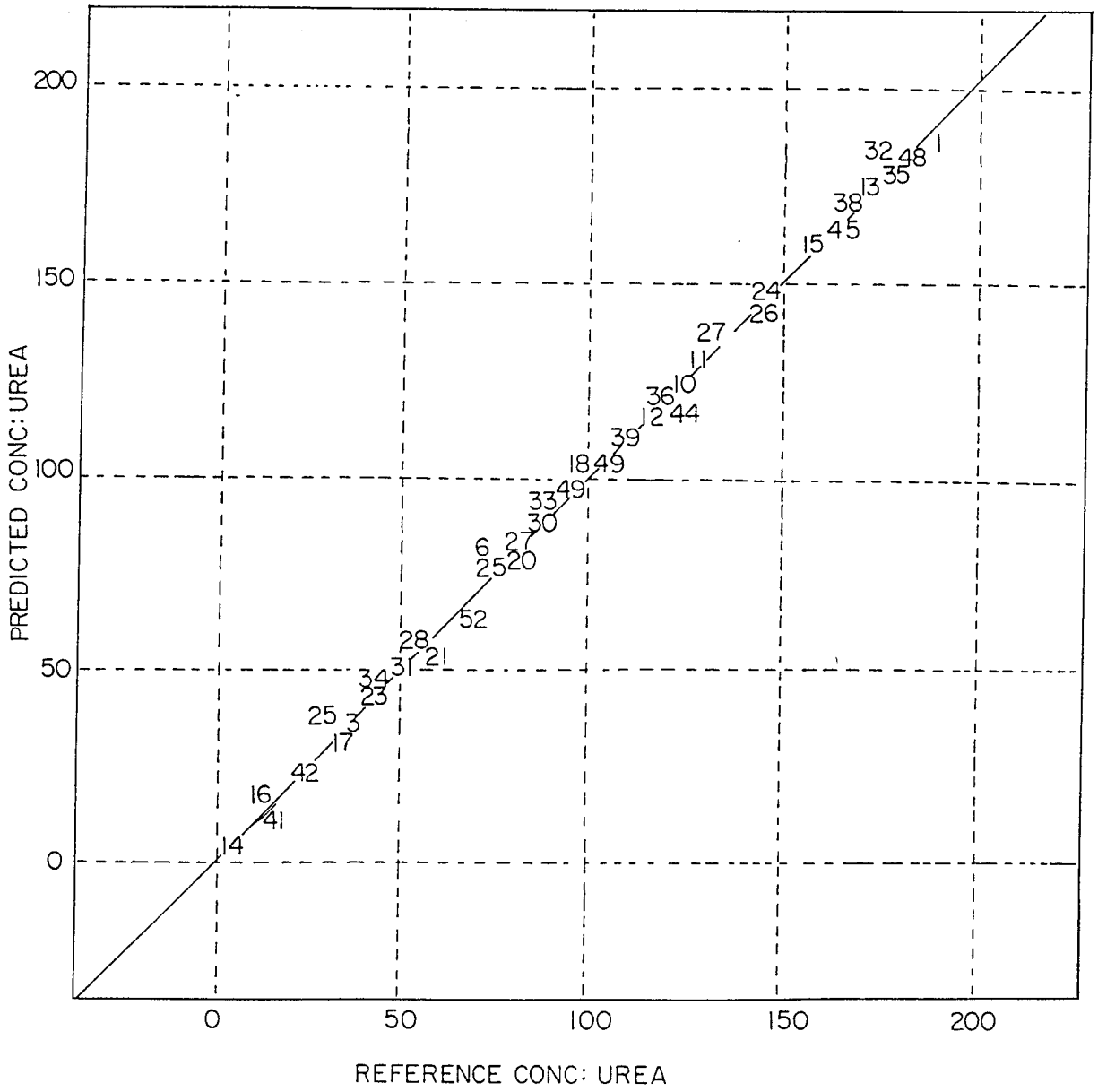
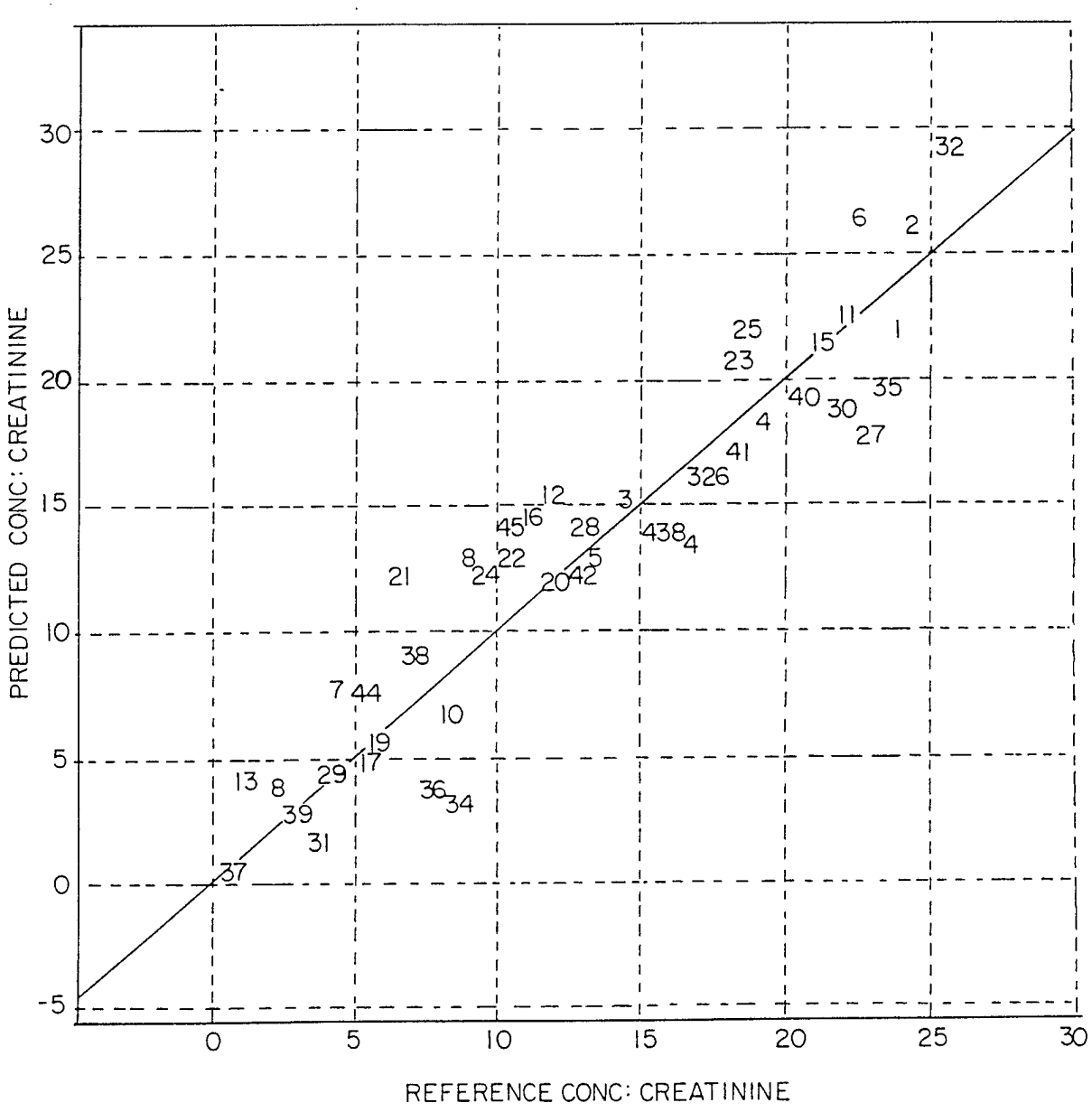


Fig.8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REFERENCE CONC: CREATININE
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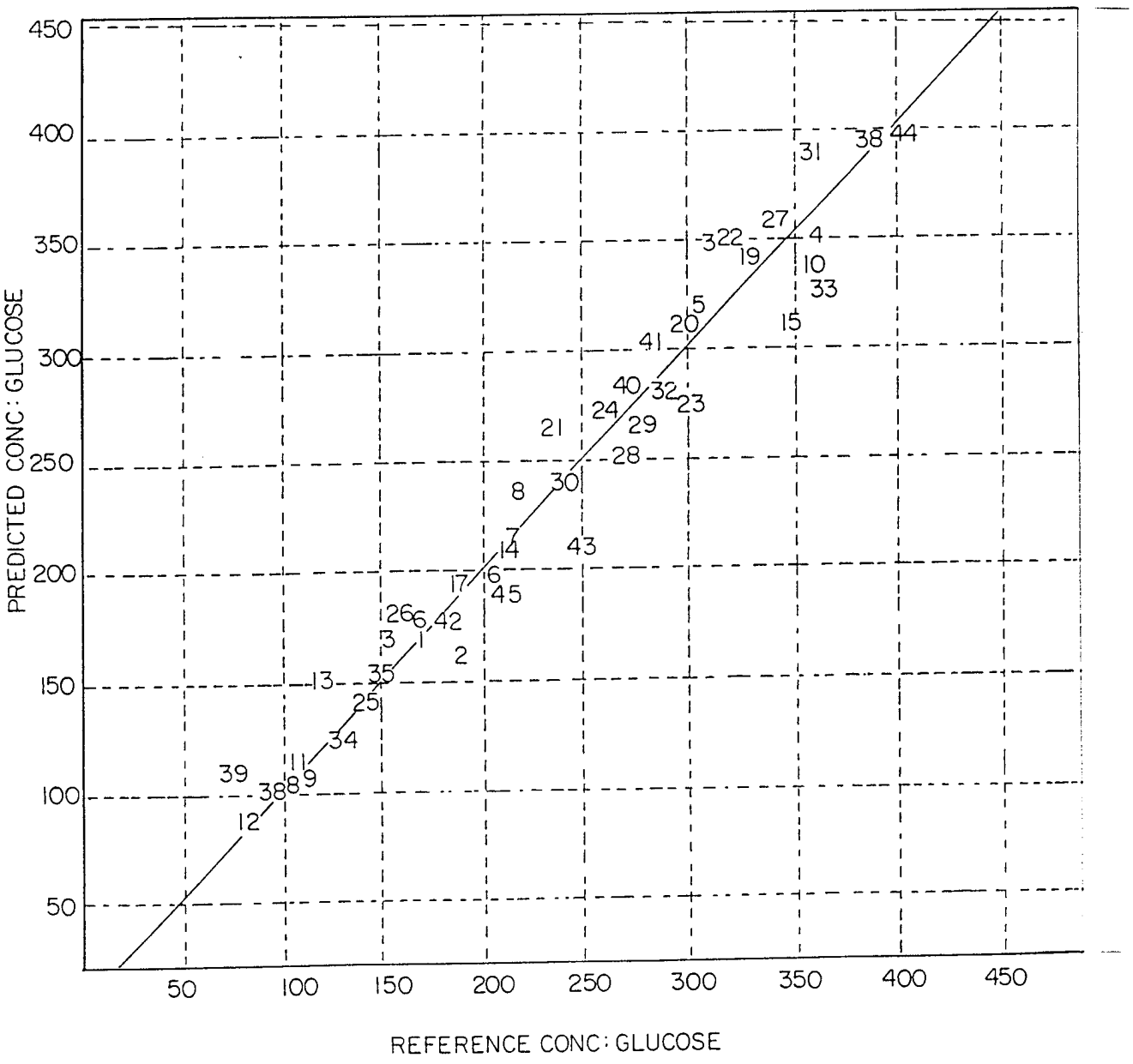
25
20
15
10
5
0
-5
0
5
10
15
20
25
30

Fig.9


PREDICTED CONC: GLUCOSE
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200
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300
350
400
450

Fig.10

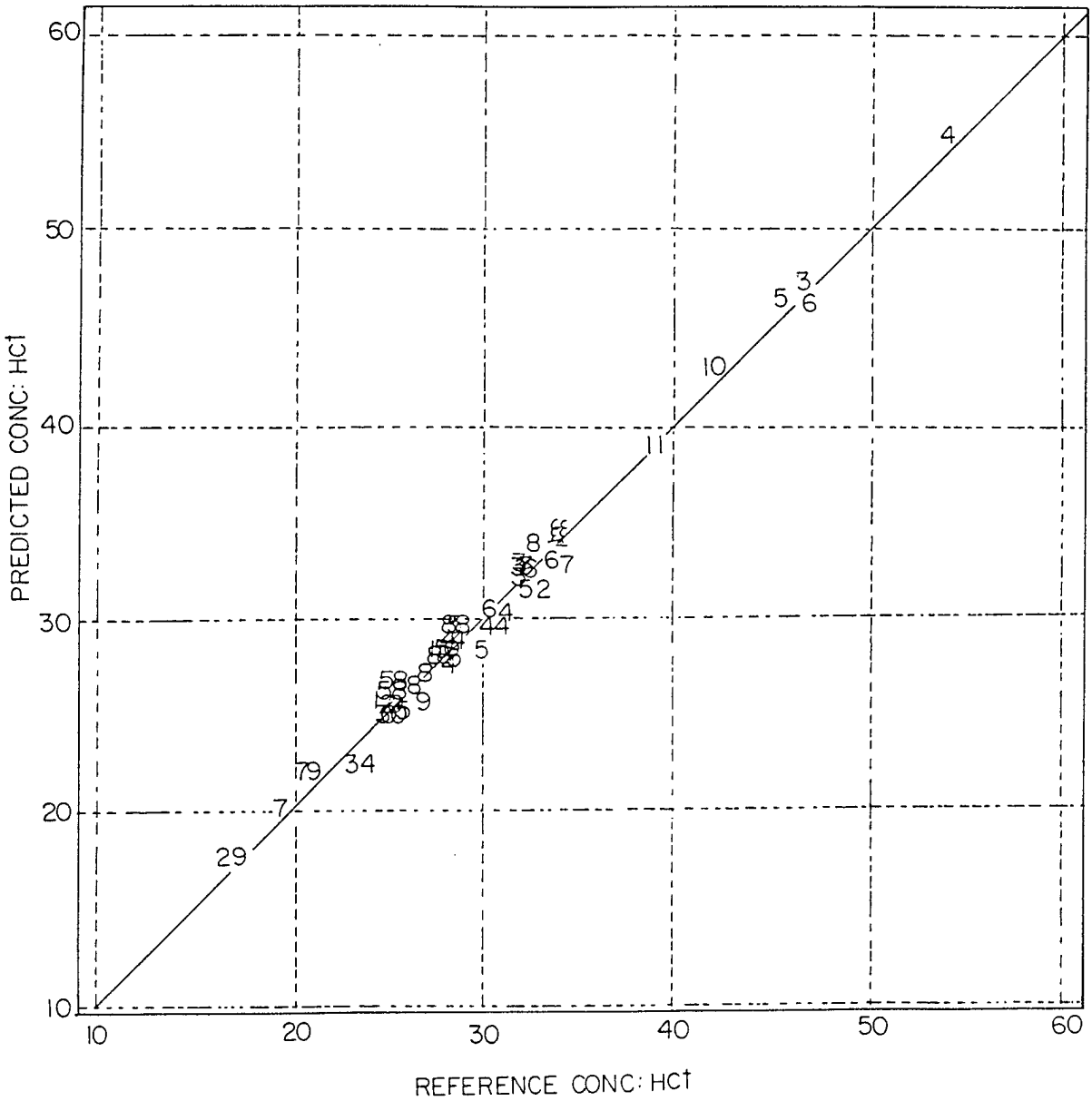


Fig. 11

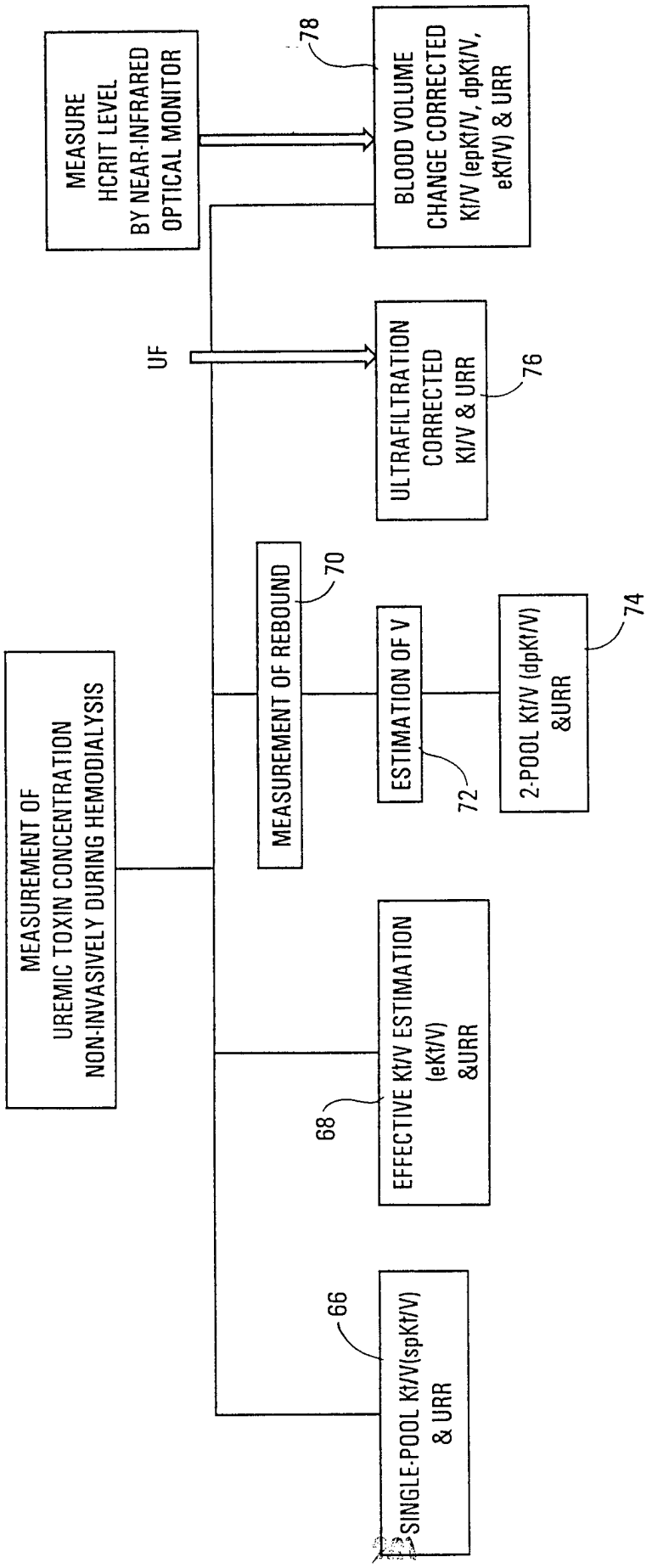

MEASUREMENT OF UREMIC TOXIN CONCENTRATION NON-INVASIVELY DURING HEMODIALYSIS
MEASURE HCRIT LEVEL BY NEAR-INFRARED OPTICAL MONITOR
78
BLOOD VOLUME CHANGE CORRECTED Kt/V (epKt/V, dpKt/V, eKt/V) & URR
UF
ULTRAFILTRATION CORRECTED KI/V & URR
76
MEASUREMENT OF REBOUND
70
ESTIMATION OF V
72
2-POOL Kt/V (dpKt/V) &URR
74
EFFECTIVE Kt/V ESTIMATION (eKt/V) &URR
68
SINGLE-POOL Kt/V(spKt/V) & URR
66

Fig.12

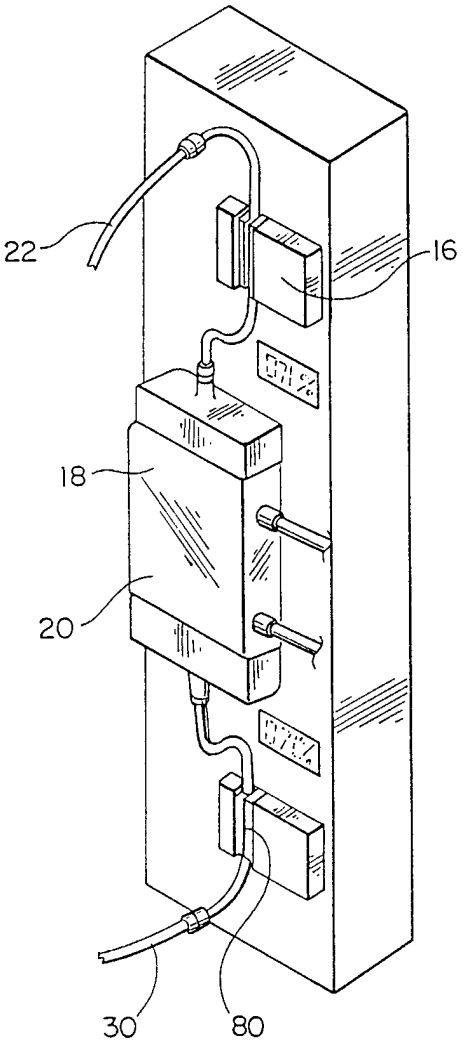


Fig.13

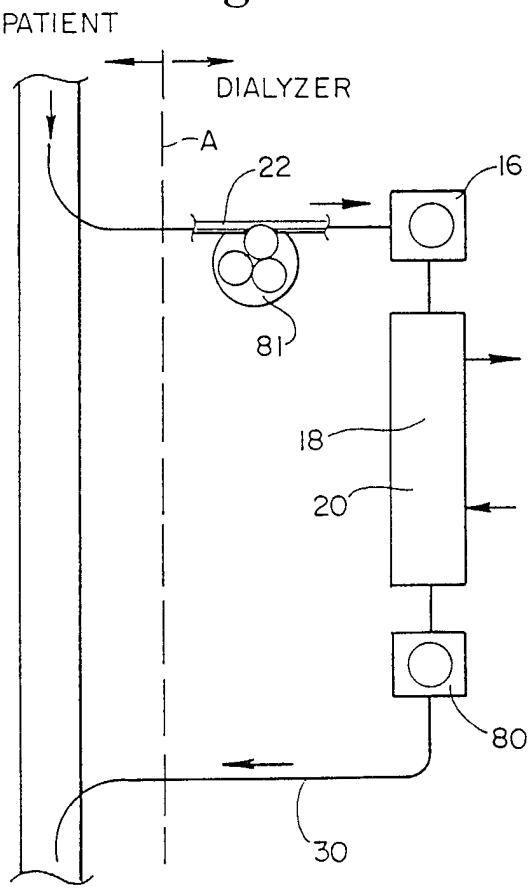
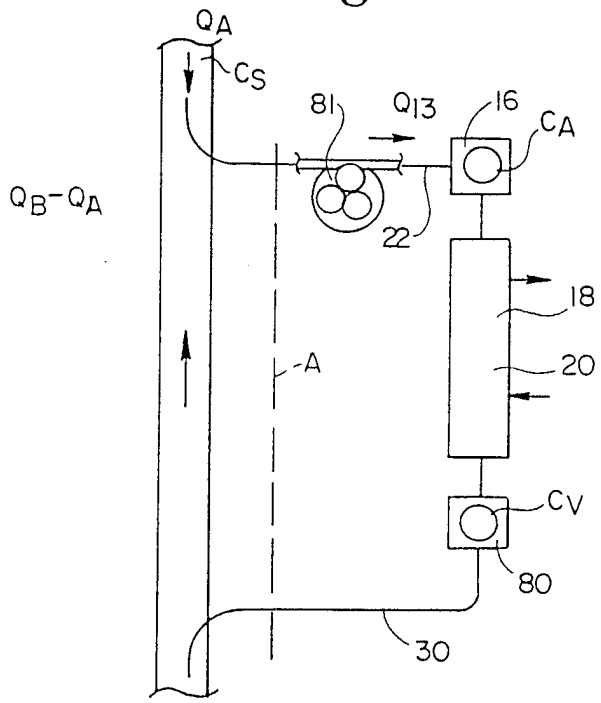


Fig.14


Q_A
C_S
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Q_{13}
16
C_A
Q_B-Q_A
22
18
A
20
C_V
80
30

Fig.15

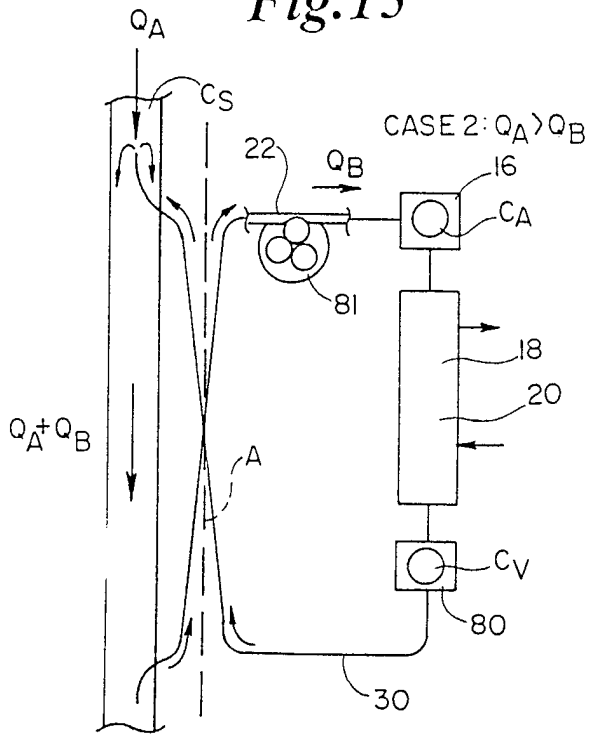

Q_A
C_S
CASE 2: $Q_A > Q_B$
22
Q_B
16
C_A
81
18
20
Q_A+Q_B
A
C_V
80
30

Fig.16a

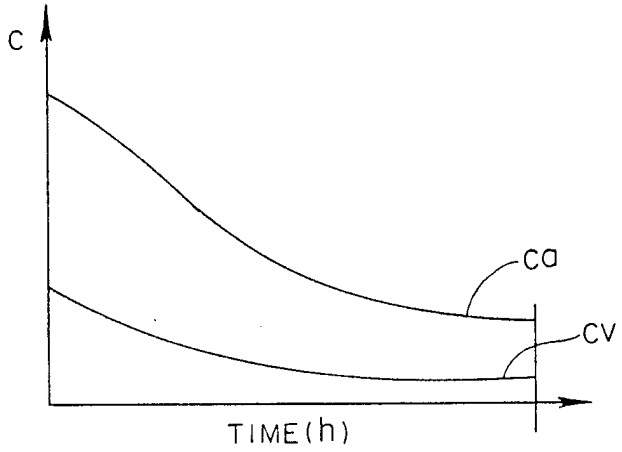


Fig.16b

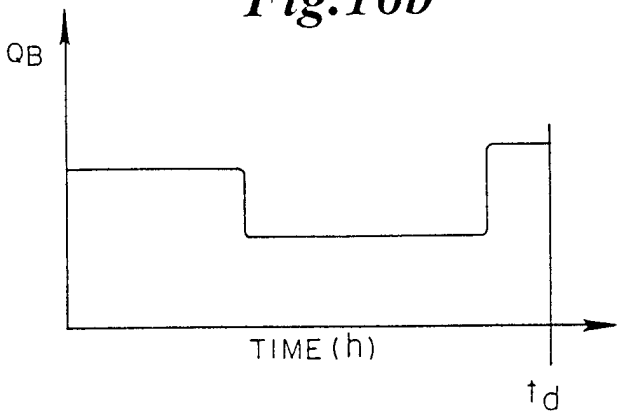
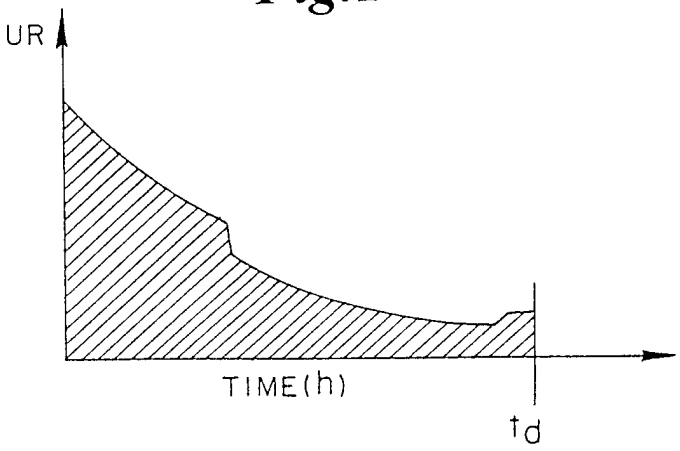


Fig.16c



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19869

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/00
US CL :356/39; 600/322; 604/6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 356/39; 600/316, 322, 326, 333; 604/4-6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,427,889 A (MULLER) 24 January 1984, entire document.	5, 6, 15-20
Y	US 5,331,958 A (OPPENHEIMER) 26 July 1994, col. 9 lines 24-35.	3, 4
A	US 5,351,686 A (STEUER et al) 04 October 1994, col. 4 line 7 to-col. 6 line 24.	1-39
X --- Y	US 5,366,903 A (LUNDSGAARD et al) 22 November 1994, col. 3 line 16 to col. 5 line 6.	1, 2, 5, 6, 15-17, 19, 20 --- 3, 4
A,P	US 5,681,273 A (BROWN) 28 October 1997, entire document.	7-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
19 FEBRUARY 1998

Date of mailing of the international search report
10 MAR 1998

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