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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 : G01N 27/30	A1	**(11) International Publication Number:** WO 85/ 02257 **(43) International Publication Date:** 23 May 1985 (23.05.85)

(21) International Application Number: PCT/US84/01814

(22) International Filing Date: 8 November 1984 (08.11.84)

(31) Priority Application Number: 550,360

(32) Priority Date: 10 November 1983 (10.11.83)

(33) Priority Country: US

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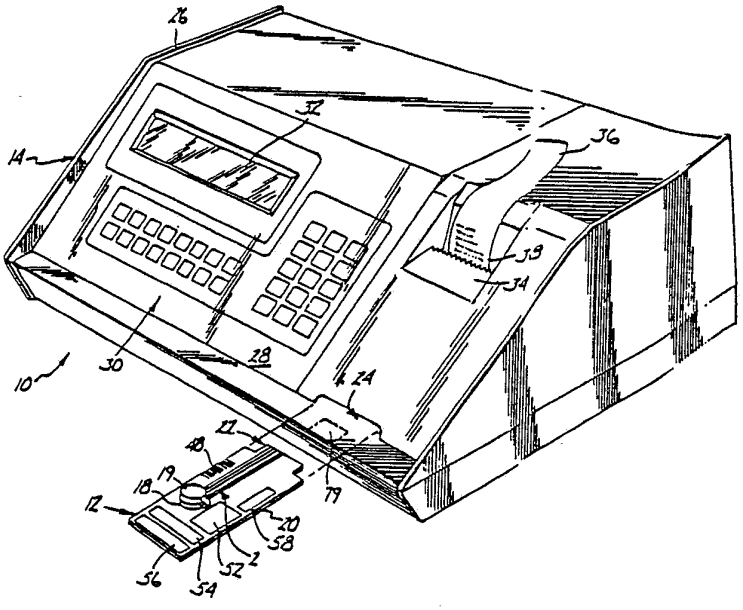
(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: CLINICAL CHEMISTRY ANALYZER

(57) Abstract

A clinical chemistry analyzer system (10) determines the concentration of selected chemicals in body fluids such as whole blood, serum, or urine. The system includes a disposable single-use sensing device (12) which has a cavity for receiving and holding samples of the body fluid. At least one species selective sensor (16A-16D) and a reference sensor (16E) are exposed to the interior of the cavity to contact the body fluid sample. The species selective sensor (16A-16D) and the reference sensor (16E) are connected to a measurement section of an analyzer (14) by inserting the sensing device into a receptacle (24) of the analyzer (14). The measurement section measures a signal from the species selective sensor (16A-16D) and the reference sensor (16E) which is a function of concentration of the selected chemical species in the sample. A concentration determining section of the analyzer (14) then determines the concentration of the selected chemical species in the sample based upon the measured signal, and the concentration is displayed and printed out.



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CLINICAL CHEMISTRY ANALYZER

REFERENCE TO COPENDING APPLICATION

Reference is made to copending applications entitled "Disposable Single Use Sensing Device for Clinical Chemistry Analyzer" by R. Little and R. Laska, Serial No. 550,313, filed November 10, 1983, and "Multiple Species Group Disposable Sensing Device for Clinical Chemistry Analyzer" by M. Knudson, W. Sembrowich and S. Carlson, Serial No. 550,361, filed November 10, 1983 which are assigned to the same assignee as the present application.

BACKGROUND OF THE INVENTION

1. Field of the Invention.

The present invention relates to medical devices. In particular, the present invention relates to clinical chemistry analyzers which are used for the measurement of medically significant substances in body fluids.

2. Description of the Prior Art.

The increasing sophistication in the treatment of disease in recent years has led to the need for diagnostic instrumentation that will effectively gather accurate information on the patient before treatment begins. A critical component of this information gathering involves blood analysis for determining the presence and concentration of particular chemicals in the blood.

The methods by which chemical data are gathered for accurate medical diagnosis constitute a branch of medical science called clinical chemistry. Currently there are three major methods which are commonly used to measure the level of chemicals in

blood or other body fluids. These methods are: optical, flame photometry, and ion selective electrodes.

The optical methods (which are sometimes referred to as spectrophotometric methods) operate on the principle that when specific reagents are mixed with a sample of the body fluid, a reaction takes place which allows the measurement of the chemical of interest by measuring the change in wavelength of light transmitted by the sample. The clinical chemistry analyzer systems which use an optical method have typically operated by either mixing the sample with a prepackaged amount of reagents or by allowing the mixing of the sample with the reagents through various tubing and mixing operations.

In flame photometry, the sample is consumed in a flame. The specific light produced by a given chemical of interest during the combustion process is used to determine the level of that chemical in the body fluid.

Ion selective electrode measurement methods use electrodes having membranes that selectively interact with chemical ions of interest. These methods involve a potentiometric, amperometric or other electrical measurement which is a function of the concentration of the ion of interest in the sample.

The field of ion selective electrodes and their related art has been the subject of extensive study. The current state of the art has addressed some of the major problems in ion selective electrode development. These problems were found especially in the electrodes which can be referred to as

barrel-type electrodes and membrane or glass electrodes. The major shortcomings of these prior art electrodes include cost, fragility, and reproducibility. Coated wire electrodes comprising a metal (e.g. platinum) wire coated with a layer of a polymer (e.g. polyvinylchloride) solution mixed with an electroactive species have been developed to solve some of these problems. Coated wire sensors are discussed, for example, in Moody, G.J. and Thomas, J.D.R., "Poly (Vinyl Chloride) Matrix Measureance Ion-Selective Electrodes", Chapter 7, Ion Selective Electrode Methodology, Vol. I; Editor: A.K. Covington (1979); Cattral and Frieser, Anal. Chem., 43:1905 (1971); and Ion-Selective Electrodes in Analytical Chemistry, Vol. 1; Editor H. Frieser. However, both those ion selective electrodes which include internal reference and those which do not include an internal reference exhibit significant drift. Electrodes which include an internal reference are described in Stworzewicz, T., Cyapkiewicz, J., and Lesko, M., at The Symposium on Ion Selective Electrodes in Mutrafured, Hungary, October 1972 (proceedings reported in Ion Selective Electrodes, edited by Pungor, E., Budapest 1973) and in U.S. Patent 4,214,968 by Battaglia, C.J., Change, J.C., and Daniel; D.S. The Battaglia et al U.S. patent attempts to correct for the drift problem by utilizing a system which makes the drift more or less predictable. This is attempted in a way such that the drift can be "zeroed out" by calibration with a standard solution on an identical electrode connected to the test electrode by a salt bridge. This standard electrode acts as a combined reference and

standardizer which is done with each test as the system is used at the user site.

One of the major causes of this drift in ion selective electrodes is capacitance effects which are uncontrolled and therefore "float". This floating or changing capacitance causes drift, error and the need for standardization and restandardization. These capacitance effects are related to three significant deficiencies in the prior art ion selective electrodes.

First, the spatial relationship of the reference electrode to the sensing electrodes are not fixed one to another.

Second, these electrodes are constructed in multiple layers over the conductor and each of these layers may have varying characteristics which give varying capacitances and therefore uncontrollable changes in capacitance.

Third, in certain multi-layer electrodes with a dried hydrophlic layer interposed between the sensing electrode and the conducting layer, the capacitance changes continuously with time as the dried hydrophilic layer changes its state of hydration during a test. There are still other types of electrodes which have various layers which are not fixed; these can be physically deformed as well, causing additional, uncontrollable changes in capacitance.

One method which has been attempted to overcome this drift is to have a reference electrode and a sensing electrode incorporated together and then use a reference solution and salt bridging to make the drift characteristics identical between two

electrodes and therefore make it easier to correct for this drift as in the above-cited Battaglia et al U.S. patent. This requires very complicated manufacturing techniques and very expensive instrumentation to analyze the various changes in voltage with time and make a reliable measurement.

In the past, the clinical chemistry analyzers using optical, flame photometry or ion selective electrode methods have tended to be large in size, expensive, and complex to operate. Analyzers using optical techniques or ion selective electrodes have been expensive to acquire due to the complexity of the mechanical systems and the nature of the exacting measurement required. They have also needed trained operators to continually monitor and evaluate the measurements, have required exhaustive and frequent maintenance, and have required frequent calibration.

Analyzers using flame photometry have also required trained operators and an extremely high amount of maintenance. In addition, flame photometers have required a source of propane and an open flame, which is undesireable for safety reasons.

In general, only large medical institutions have been able to afford the purchase of clinical chemistry analyzers. Smaller hospitals, clinics and physician group practices usually have had to employ centralized hospital laboratories or commercial laboratories to do their chemical tests. These laboratories have grown substantially in the last decade with the increased emphasis on measurement of medically significant substances in the blood and other body fluids as a part of the physician's

diagnosis prior to treatment.

In the past, basic blood chemistry tests have often been very time consuming. When a physician has required a basic blood test, a blood sample has been taken and then sent to a laboratory for analysis. Receiving the results of the test from the laboratory in nonemergency cases has taken from one hour to several days. In the meantime, the patient may have left the clinic and then had to return later or be telephoned to consult with the physician on the results of the test. This procedure has been inconvenient and medically inefficient for both the physician and the patient.

There is a strong need for clinical chemistry instrumentation that can be readily available to all physicians who desire to conduct selected basic chemistry tests without delay and at a reasonable cost. This need extends to individual doctor's offices, physician group practices, hospitals for bedside applications, operating and emergency rooms, cardiac and intensive care units, nursing homes, ambulances and emergency vehicles, and in centralized laboratories for immediate ("stat") use.

This need for improved clinical chemistry instrumentation, however, requires an analyzer which is less expensive to acquire, is easier to operate, requires less maintenance, eliminates the need for an open flame, eliminates the need for constant calibration and verification of measurements, reduces drift to a negligible level, eliminates need for calibrated reagents, is portable enough to allow its use where required, and uses whole blood so that the

time consuming step of centrifuging blood samples is eliminated and the amount of blood required for testing is reduced. The prior art clinical chemistry analyzers, however, have been unable to meet the requirements.

SUMMARY OF THE INVENTION

The present invention is an improved clinical chemistry analyzer system which utilizes single-use sensing devices in conjunction with an analyzer to determine concentration of selected chemical species in body fluids. The single-use sensing device receives and holds a sample of the body fluid, and is inserted into a receptacle of the analyzer when a measurement of the concentration of selected chemical species is to be made. Once the measurement has been made, the single-use sensing device is removed from the analyzer receptacle and can be discarded.

The single-use sensing device preferably includes a cavity for holding the sample, a carrier, at least one species sensor, a separate reference sensor, and connection means. The species sensor and the reference sensor are supported by the carrier in a fixed spaced relationship so that the species sensor and the reference sensor extend into the cavity to contact a sample of the body fluid contained in the cavity. The connection means engages the receptacle of the analyzer and connects the species sensor and the reference sensor to the analyzer.

Each species sensor has a species selective portion which contacts the sample of body fluid and interacts selectively with a selected chemical

species to cause a characteristic of the species sensor to vary as a function of concentration of that selected chemical species in the sample. The reference sensor has a portion which contacts the sample but which does not interact selectively with the selected chemical species so that the corresponding characteristic of the reference sensor does not vary as a function of a concentration of the selected species in the sample.

The analyzer includes means for deriving a signal from the species sensor and the reference sensor which represents a measured difference in the characteristics of the sensors. The analyzer also includes means for determining concentration of the selected chemical species based upon the measured difference. In some embodiments, the analyzer also includes means for calculating other values based upon the concentration.

In preferred embodiments of the present invention, the analyzer includes output means for providing an output in human readable form which indicates the concentration of the selected chemical species in the sample or other calculated values of clinical interest. This output means preferably includes both a visual display and a device (such as a printer) for providing a permanent printed record of the concentration. In some embodiments, the output means also includes a communication device for transmitting the output to other equipment (such as a digital computer) for further analysis or storage.

The single-use sensing device preferably includes machine-readable indicia which identify the particular sensors contained in the sensing device

and their characteristics. In these embodiments, the analyzer includes a reader which reads the indicia when the single-use sensing device is inserted in the receptacle. The identification information conveyed by the indicia preferably includes the location and identity of each sensor supported by the carrier, calibration data for each species sensor, and a lot or serial number of the sensing device. The analyzer uses the information which has been read from the machine-readable indicia by the reader in determining the concentration and in providing an output in human readable form.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of a preferred embodiment of an analyzer and a disposable sensing device which form the clinical chemistry analyzer system of the present invention.

Figure 2 is a top view of the disposable sensing device of Figure 1.

Figure 3 is an electrical block diagram of the analyzer of Figure 1.

Figures 4A-4D are perspective views showing other preferred embodiments of the disposable sensing device of the system of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

1. Analyzer System 10

The preferred embodiment of clinical chemistry analyzer system 10 of the present invention is a compact, self-contained portable system which facilitates usage in a physician's office, an operating room or a clinical chemistry laboratory to measure concentrations of chemicals in blood and other body fluids. Analyzer system 10 includes a

disposable single-use sensing device 12 which is used in conjunction with analyzer 14. Disposable sensing device 12 (which is shown in further detail in Figure 2) includes a plurality of sensors 16A-16E which interact directly with chemicals of interest in the body fluid to provide signals which have a known relationship to concentration of the chemicals of interest in the body fluid. A sample of body fluid is maintained within cavity 18. Sensors 16A-16E have their active areas exposed to the interior of cavity 18, so as to interact with the sample of body fluid contained within cavity 18. Cover 19 seals cavity 18 to prevent any spilling or evaporation of the sample and any loss of blood gases from the sample. In the embodiment shown in Figures 1 and 2, carrier 20 (which is in the form of a flat, generally rigid card) supports sensors 16 and cavity 18. Conductors 21A-21E extend between and interconnect sensors 16A-16E and electrical contacts 22A-22E, respectively. Electrical contacts 22A-22E are located along a front edge of carrier 20 to make electrical connection with the circuitry of analyzer 14 when disposable sensing device 12 is inserted into receptacle 24 of analyzer 14. The particular embodiment of disposable sensing device 12 shown in Figures 1 and 2 is described in further detail in the previously mentioned copending patent application entitled "Disposable Single Use Sensing Device for Clinical Chemistry Analyzer", and that description is hereby incorporated by reference.

Analyzer 14 includes a housing 26 which contains all of the electronic circuitry used to calculate concentrations of the chemical species of

interest based upon the signals from sensors 16A-16E of disposable sensing device 12. In the preferred embodiment shown in Figure 1, analyzer 14 is of a size which is suitable for desk or bench top use, or for use on a cart. Front panel 28 of analyzer 14 includes keyboard 30 and display 32 which allow an operator to interact and control the operation of analyzer 14. Analyzer 14 also preferably includes printer 34 within housing 26. Printer 34 provides a hard copy printout of the output of analyzer 14 (which preferably includes calculated concentrations and other values, warnings of abnormalities, time and date, lot number and/or serial number of sensing device 12, and patient name or identification number). This printout is provided on print paper 36 which is fed out of opening 38 in analyzer housing 26.

When disposable sensing device 12 is inserted into receptacle 24 of analyzer 14, contacts 22A-22E make electrical contact with receptacle connectors 42 of analyzer 14. The electrical circuitry of analyzer 14 measures signals from sensors 16A-16E of sensing device 12. Based upon the measured signals, analyzer 14 calculates concentration of the chemicals of interest which have been sensed and, in some cases, other values based upon these concentrations (e.g. sodium-to-potassium ratio and anion gap). The results of those calculations are displayed on display 32 and are printed out by printer 34 on paper 36. Once the calculations have been completed and the results displayed and printed, disposable sensing device 12 is removed from receptacle 24 and is discarded.

2. Single-Use Sensing Device 12

In a preferred embodiment of the present invention shown in Figure 2, sensing device 12 includes four species-selective electrode sensors 16A-16D and a reference electrode 16E which are in the form of thin conductive films deposited on carrier 20, and which are connected by conductors 21A-21E to contacts 22A-22E. Sensors 16A-16E are located in cavity 18 (which is shown in phantom in Figure 2). Each species-selective sensor 16A-16D has a sensor active area within chamber 18 which has a species-selective coating 44A-44D, respectively, which selectively interacts with a particular chemical of interest in the sample of body fluid contained within chamber 18. The coating 44A-44D preferably includes a polymer and an electroactive species. The polymer serves the functions of creating a membrane over the sensor active area and immobilizing the electroactive species next to the electrically conductive surface of the metallic film of the respective sensors 16A-16D. The polymer is, for example, polyvinyl chloride, an epoxy, or a polystyrene which is mixed with an electroactive species in a homogenous fashion to provide a membrane through which the chemical species of interest can diffuse.

The electroactive species confers the specificity to the sensor. The electroactive species of the coating 44A-44D depends, of course, upon the particular chemical species of interest which is to be sensed. The electroactive species must interact with the chemical species on a selective basis in a known and predictable manner. For example, for a

calcium ion (Ca++) sensor, a salt, (calcium di-(octyl-phenyl) phosphonate + dictylphenyl-phosphonate) is one electroactive species which shows good response in the physiological concentration range of 10^{-5} to 10^{-2} Molar. For a potassium ion (K+) sensor, an ionophore (valinomycin) is one effective electroactive species. An ionophore is a compound which has the ability to bind a particular ion and transport it across a membrane layer. The binding is detected in the form of a potentiometric charge. Those skilled in the art of ion selective electrodes will recognize there are a variety of ionphores and other compounds which will accomplish the same end.

In some embodiments of the present invention, a spreading layer (not shown) overlies each of the coatings 44A-44D. The purpose of the spreading layer is to ensure that the sample contacts the entire surface of coating 44A-44D uniformly.

The active area of reference sensor 16E either has no coating at all, or has a coating 47 which is not specific to the particular chemical species of interest. Reference sensor 16E provides a reference from which an electrical measurement can be made by analyzer 14. By measuring an electrical characteristic (e.g. potential, current) between each of the species sensors 16A-16D and reference sensor 16E, a signal which is a function of chemical concentration of the particular chemical species of interest being sensed by sensors 16A-16D can be obtained. Based upon these signals, the electrical circuitry of analyzer 14 calculates the concentration of the chemical species of interest being measured by sensors 16A-16D.

One of the major improvements achieved with the present invention is that the individual sensors 16A-16E are of a simple construction which permits use of techniques common to the electronic and anodizing industries to coat conductors with an ion selective layer. Sensors 16A-16E do not require multiple layer construction over the conductor and do not incorporate layers which result in changing capacitance.

In fact, in other embodiments of the present invention, the conductors and the species selective coating of sensors 16A-16D are integral rather than having been formed by separate depositions.

Because of the simple construction, deposition of the conductors and the coatings can be very closely controlled so that the spatial relationship between reference sensor 16E and any number of species sensors 16A-16D can be very precisely controlled. Therefore, the only capacitance inherent in the system is the capacitance of the sensor 16A-16E itself. This capacitance can be very easily controlled because it is known and it does not change with time, space relationships or hydration state and, therefore, no complicated techniques (such as salt bridging or reference solutions) are required. This allows sensors 16A-16E to be inexpensive enough to be disposable and have multiple species testing capabilities on the same device 12. No previous technology developed in this field allows for this type of manufacturing process, control and inexpensive measurement technology.

Another important feature of the present invention is that the use of disposable sensing

device 12 with analyzer 14 does not require operator calibration (although some calibration capability can be provided as described later, to allow the operator to verify proper operation using a reference solution and make small calibration adjustments). This makes analyzer system 10 of the present invention easier and less time-consuming to use. In the past, the need for calibration has been particularly critical because the sensing equipment could become contaminated after a number of tests and therefore could produce erroneous results. Even if the sensors did not become contaminated, their characteristics often changed with repeated tests, so that frequent calibration was critical to accurate measurements of chemical concentrations.

With the present invention, disposable sensing devices 12 are factory calibrated, and then are used only one time. As a result, the problems of contamination or variation in sensor characteristics due to use of the same sensor for repeated tests are eliminated. In preferred embodiments of the present invention, at least one sensing device 12 from each batch or lot of sensing devices 12 is factory-tested by exposing sensors 16 of that device to a solution having known concentrations of each of the species to be sensed. Based upon the signals produced by sensors 16 during this calibration process, a calibration factor is determined for each of the species selective sensors 16A-16D. The calibration data are recorded in the form of machine-readable indicia (such as on coded label 48 as part of a bar code) for all sensing devices 12 of that lot. When sensing device 12 is inserted into receptacle 24 of

analyzer 14, coded label 48 is read by code sensor 50 of analyzer 14, and the calibration data are stored by analyzer 14 for use in calculating concentrations of the chemical species of interest.

Although the embodiment of the present invention shown in Figure 2 shows four species selective sensors 16A-16D together with a reference sensor 16E, it will be understood that the number of species selective sensors can vary from as few as one to ten or more. The particular number of contacts 22 will, of course, vary depending upon the number of sensors 16, and the size of cavity 18 may be larger in those devices containing a large number of sensors 16 in order to maintain the sensors 16 in fixed spaced relationships.

Still another important advantage of the present invention is that different disposable sensing devices 12 having different groups of species selective sensors 16A-16D can be used with the same analyzer 14. In these embodiments, each of the different types of disposable sensing device 12 includes machine-readable, indicia, such as the bar code carried by coded label 48, which includes an identification of the particular sensor associated with each of the electrical contacts 22. As discussed later, coded label 48 also contains calibration data and also preferably includes a lot and/or serial number identification of sensing device 12. When sensing device 12 is inserted into receptacle 24 of analyzer 14, code sensor 50 (Figure 3) reads coded label 48 and provides signals to the electronic circuitry of analyzer 14 which indicates the particular chemical species of interest being

sensed by each sensor carried by that sensing device 12.

In other embodiments of the present invention, the identification of the particular sensors 16A-16E contained in device 12 can be provided to analyzer 14 by other means. For example, different patterns of contacts 22A-22E can designate different groups of sensors 16A-16E.

In order to assist the physician or other medical personnel in selecting the particular sensing device having sensors for the group of chemical species which is desired, each sensing device 12 also preferably includes a "TESTS" identifier printed block or label 52 which lists the particular chemical species which are sensed. In some preferred embodiments of the present invention, identifier label 52 is also color coded to simplify selection. The species identified by label 52 preferably are factory printed.

In the preferred embodiment shown in Figure 2, sensing device 12 also contains a "PATIENT NAME" printed block or label 54, a "PATIENT NUMBER" printed block or label 56, and a "LOT NO." printed block or label 58 (which preferably carries a factory printed lot number and/or serial number).

The disposable sensing devices 12 of the present invention preferably provide groups of sensors 16 which allow simultaneous testing of concentrations of a group of chemical species which together are useful to a physician or other medical personnel. With the present invention, therefore, tests which are normally performed for patients having particular symptoms or conditions can be

performed simultaneously. The groups of species include but are not limited to an "Electrolyte Screening" group, a "Diabetic" group, a "Renal" group, a "Dialysis" group, a "Pregnancy" group, a "Heart" group, an "Emergency" group, a "Neonatal" group, a "Blood Gas" group, an "Operating Room" group, and a "Cancer" group. The species sensors used in each of these groups and purposes of each group are described in detail in the previously mentioned patent application "Multiple Species Group Disposable Sensing Device for Clinical Chemistry Analyzer", and that description is incorporated by reference.

3. Analyzer 14

Figure 3 is an electrical block diagram of a preferred embodiment of analyzer 14. In this embodiment, analyzer 14 includes keyboard 30, display 32, printer 34, connectors 42, code sensor 50, digital microprocessor 60, program memory 62, nonvolatile data memory 64 volatile data memory 66, code reader interface 68, signal conditioning/driver circuit 70, analog multiplexer 72, high stability reference 74, analog-to-digital (A/D) converter 76, temperature sensor 77, battery-powered clock/calendar 78, and communication interface 80.

Keyboard 30 allows the operator to interact with analyzer 14 by providing input signals to digital microprocessor 60. In preferred embodiments of the present invention, keyboard 30 includes keys which allow the operator to choose particular operations to be performed by analyzer 14, includes keys for entering data such as patient identification numbers and critical concentration limits or ranges

which should be flagged by analyzer 14 and includes keys for selecting the units of measurement to be used by analyzer 14.

Digital microprocessor 60 controls the operation of analyzer 14 and interacts with the other electronic circuitry based upon a stored program contained in program memory 62. Microprocessor 60 calculates the concentrations of each of the chemical species of interest and other values based upon those concentrations, and provides outputs through display 32, printer 34 and communication interface 80.

When sensing device 12 is inserted into receptacle 24 of analyzer 14, contacts 22 of sensing device 12 make electrical contact with connectors 42 of analyzer 14, thus connecting sensors 16 to signal conditioning circuit 70. The output of signal conditioning circuit 70 is an analog signal for each of the species sensors. Analog multiplexer 72 receives the output from signal conditioning circuit 70, together with a high stability reference signal from high stability reference 74. The signals from analog multiplexer 72 are sequentially supplied to A/D converter 76, which samples the analog signals and converts them to digital values. These digital values are supplied by A/D converter 76 to digital microprocessor 60.

In preferred embodiments of the present invention, temperature sensor 77 also provides a signal to multiplexer 72 which is supplied to A/D converter 76, and converted to a digital value which indicates the temperature. This temperature value is used by microprocessor 60 in its concentration calculations and in controlling operation of heater

79 (which is located under cavity 18 when sensing device 12 is inserted in receptacle 24). Heater 79 is operated for those species measurements which require elevated temperatures above room temperature. In the embodiment shown in Figure 3, temperature sensor 77 (which is, for example, a thermistor) is mounted in analyzer 14 so that the temperature value produced is representative of ambient temperature and thus approximates the temperature of the sample. In other embodiments where greater accuracy in the temperature measurement is required, temperature sensor 77 is mounted on and forms a part of disposable sensing device 12. In those embodiments, temperature sensor 77 may be in contact with the sample.

A/D converter 76 is basically a ratiometric device - that is, the digital output represents the ratio of the input voltage to an internal reference voltage. As such, the accuracy of the digital output is dependent on the accuracy of the internal reference voltage. To ensure validity of the measurements made by analyzer 14, a second independent stable reference source (high stability reference 74) is periodically measured (for example once each time device 12 is inserted). The value determined by A/D converter 76 for the independent reference voltage from high stability reference 74 is compared with the stored proper value. A variation in the measured value would indicate that either A/D converter 76 and associated elements are producing incorrect results, or that the high stability reference 74 is in error. In either case, the use of high stability reference 74 provides a high degree of

assurance that the analog portions of analyzer 14 are functioning properly.

Code sensor 50 reads coded label 48 carried by sensing device 12. Code reader interface 68 receives the output signals from code sensor 50, and converts those signals to digital data which represent the information stored on coded label 48. As discussed previously, the information carried by coded label 48 preferably includes an identification of each of the sensors 16 of sensing device 12, calibration factors for those sensors, and a lot number for sensing device 12. Although code reader 50 is preferably mounted in analyzer 14, in some embodiments it is or includes a hand-held code reader wand which permits the operator to perform the code reading function.

In the particular embodiment of the present invention illustrated in the Figures, each of the species selective sensors 16A-16D provides a signal in the form of a potentiometric difference between that sensor 16A-16D and reference sensor 16E which is a function of the concentration of that particular species in the sample of body fluid. In the case of ionic species, the relationship between the potentiometric difference and the ion concentration is described by the well-known Nernst equation. For other types of chemical species, other relationships between the concentration and the signal derived from sensors 16 are exhibited and thus are used in the calculation of concentration. With the present invention, the particular relationship is not critical, so long as it is a predictable relationship which can be used by digital microprocessor 60 in

converting the data from A/D converter 76 to a concentration value.

By knowing the identity of the particular species sensor 16A-16D (based upon data from code reader interface 68) which corresponds to a particular signal from A/D converter 76, microprocessor 60 selects the particular known relationship for that sensor, and converts the sensor data value to a concentration value. This process is repeated for each of the sensor signals. Digital microprocessor 60 also uses the calibration data which was read from coded label 48 and the selected units of measurement (as selected through keyboard 30) in the concentration calculation. As a result, the resulting concentration value represents the concentration based upon the sensor signal, as corrected by the factory-determined calibration factor.

In some cases, other values which are based upon the concentration values are also of interest to the physician or other personnel. Examples of such calculated values are the sodium-to-potassium ion ratio and anion gap (which is the difference in concentration of positive ions, such as sodium and potassium and negative ions, such as chloride and bicarbonate in the blood). Microprocessor 60 uses the calculated concentration values to derive these additional calculated values.

Microprocessor 60 then compares the calculated concentration values (and/or other calculated values) with flag values stored in nonvolatile data memory 64 for the particular species of interest. These flag values of concentration

ranges or limits are selectable through keyboard 30, and can also include values of ranges which are factory-set and stored in nonvolatile data memory 64. In a preferred embodiment of the present invention, the flag values define the normal ranges for each concentration or other calculated value.

Microprocessor 60 formats the data which are provided through display 32, printer 34, and in preferred embodiments through communication interface 80 (which allows external data transfer to another computer or other external device and which preferably is an RS232 type of interface device). The data which are displayed through display 32 and printed in hard copy form by printer 34 preferably includes a patient identification, an identification of the particular chemical species, the concentration value for that species, any other calculated values, the exceeding of any flags and normal and critical ranges which are detected by digital microprocessor 60, the time of day and date (based upon a signal from clock/calendar 78) and the lot and/or serial number of disposable sensing device 12 (which is read from coded label 48 by code sensor 50).

The hard copy output from printer 34 allows a permanent record to be maintained of the measurements run by analyzer 14. Inclusion of the lot and/or serial number of each sensing device 12 provides a permanent record which can be used to trace the origin of the sensing device 12 which was used.

In the preferred embodiments of the present invention, analyzer 14 completes all measurements from the sensors 16, calculates concentrations and

other values based on concentrations, and displays the calculated values and other information within about one minute or less. Since the species sensors 16A-16D depend upon selective interaction with the species of interest, there is normally a period of time required for equilibrium between the sensor with the sample of body fluid to be reached. In preferred embodiments of the present invention, the polymer/electroactive species coating or mixture of each sensor is selected so that equilibrium has occurred within about ten to about sixty seconds after the sensing device 12 is inserted into receptacle 24 of analyzer 14. This allows the data values from A/D converter 76 to represent end points of the measurement process.

Although it is preferable to have the sensors 16A-16E reach equilibrium prior to the calculation concentrations, this is not absolutely necessary. In other embodiments in which the data values from A/D converter 76 represent intermediate sample points, microprocessor 60 calculates an end point for each sensor based upon one or more data values from A/D converter 76 for that particular sensor. Microprocessor 60 extrapolates the end point based upon data stored in memory 62, 64 or 66, and then calculates the concentration based upon the extrapolated end point and the calibration data which have been read from coded label 48.

Although calibration of analyzer 14 is essentially obviated by the use of encoded calibration data carried by sensing device 12, some embodiments of analyzer 14 include a calibration feature which permits small adjustments to be made to

analyzer 14. In these embodiments, keyboard 30 includes a calibration key which, together with the numerical keys of keyboard 30, can be used to enter calibration data for some or all of the sensors. The calibration data are derived by the operator by using one of the sensing devices 12 to sense concentrations of species in a reference sample having known concentrations. If the calculated concentration values from analyzer 14 differ from the known values, the operator can provide calibration factors which will bring the values into agreement. These calibration factors are stored and are used by microprocessor 60 in subsequent concentration calculations.

As shown in Figures 1-3, the clinical chemistry analyzer system 10 of the present invention uses a disposable sensing device 12 having solid state sensors 16 and a microprocessor-based analyzer 14 which does not require intricate mechanical design or intricate tubing or fluidics. As a result, the system of the present invention is available at a much lower cost than the prior art clinical chemistry analyzers, is light-weight and is portable. This makes the present invention applicable to a wide range of applications which have not been possible previously due to the high cost and lack of portability of the prior art clinical chemistry analyzers.

The present invention allows comparatively untrained personnel to operate the system. With the present invention, the user is prompted through display 32 in the proper use of analyzer 14.

The availability of the present invention in a doctor's office, in clinics and hospitals located away from major metropolitan areas, in an emergency room, or in an emergency vehicle or the like and the nearly instantaneous output of the results of the measurements avoids the long delays encountered in the past, when routine blood samples have been sent to a central laboratory for testing, and the results are not reported back for hours or even days. With the present invention, a physician can evaluate the results of the tests immediately, and provide diagnosis or treatment to the patient without requiring the patient to leave the doctor's office and return or call in at some later time.

Even in the central laboratory, where other larger, more complicated automated equipment is available, the present invention provides the capability of concentration measurements on a stat basis without having to start up or interrupt operation of the larger automated equipment. This is particularly advantageous at night and on weekends when demand for tests is much lower and may not justify operating a large machine for a single test.

The present invention is capable of measuring concentrations of species in whole blood. This eliminates the need for a centrifuge (and the time delays resulting from the centrifuging procedure). In addition, the volume of the blood sample reuired is less when whole blood is used.

With the present invention, maintenance is greatly reduced. Analyzer 14 preferably has a minimum of moving parts (primarily associated with printer 34), is simple in mechanical design and does

not require reagents or special plumbing like prior art analyzers. Disposable sensing device 12 eliminates the need for calibration, as well as the need for periodic replacement of sensors as required in the prior art. In addition, sensing device 12 reduces the likelihood of any accidental spilling of fluids which could contact and contaminate the electronics of analyzer 14, and eliminates the need for periodic cleaning of analyzer 14.

Another important advantage of the present invention is the ability of analyzer 14 to function with sensing device 12 having new species sensors without requiring major mechanical revisions to analyzer 14. As sensing devices 12 having new or different sensors are made available, analyzer 14 can be upgraded to accommodate those sensors simply by a change to the program software stored in program memory 62. In preferred embodiments of the present invention, the memory is segmented or sectionalized to simplify and enhance upgradability of analyzer 14 for new sensing devices 12. The upgrade modification can be made quickly and simply in the field by service personnel, without requiring that the analyzer 14 be returned to the factory.

4. Alternative Singe-Use Sensing Devices

Although Figures 1 and 2 show a particularly advantageous form of sensing device 12, it should be recognized that disposable sensing device 12 can take other forms in accordance with the teaching of the present invention. Figures 4A-4D show four alternative embodiments of the disposable sensing device of the present invention.

In Figure 4A, disposable sensing device 12A includes a circular base 100 which supports and holds four metallic wire electrodes 102A-102D in fixed spaced relationship to one another. A cylindrical tube 104 is bonded to base 100 to form a cavity 106 for receiving and holding a fluid sample.

The upper end of each of the wire electrodes 102A-102D extends upwardly into cavity 106. A coating 108A-108D is provided on the upper ends of wires 102A-102D, respectively. In this embodiment, coatings 108A, 108B and 108C are different species selective coatings which are generally similar to the coatings 44A-44C described with reference to disposable sensing device 12 of Figure 2. Coating 108D is a reference coating which is not species selective with respect to any of the species with which coatings 108A-108C selectively interact.

The lower ends of wires 102A-102D extend below base 100 to form the electrical contacts which are connected to the electrical circuitry of analyzer 14 when disposable sensing device 12A is inserted into a receptacle in analyzer 14. Due to the differences between the shape of sensing device 12 shown in Figures 1 and 2 and sensing device 12A shown in Figure 4A, the shape of the corresponding receptacle in analyzer 14 which receives and mates with sensing device 12A must be different than in the embodiment shown in Figure 1. In the case of sensing device 12A, the receptacle in analyzer 14 is in the form of a socket with female connectors for receiving wires 102A-102D rather than a slot like receptacle 24 shown in Figure 1.

Sensing device 12A also includes a coded label 48A on the outer surface of cylinder 104. Label 48A contains machine-readable indicia, such as in the form of a bar code, which provide information identifying the particular species to be sensed by each of the wire electrodes 102A-102D, calibration factors for those electrodes, and lot/serial number identification of device 12A. Coded label 48A is read by analyzer 14 when disposable sensing device 12A is inserted into the cooperating receptacle.

Figure 4B shows another embodiment of the present invention which uses coated wire electrodes as the sensor elements. In Figure 4B, disposable sensing device 12B is a two-part assembly which includes tube 120 and carrier 122. Tube 120 defines a cavity 124 for holding a sample of body fluid. Carrier 122, which is inserted into cavity 124, supports four wire electrodes 126A-126D in fixed spaced relationship to one another. The upper ends of electrodes 126A-126D extend out the top of carrier 122 and above the top edge of tube 120 to provide electrical connection between analyzer 14 and sensing device 12B. The lower ends of wire electrodes 126A-126D extend out the bottom of carrier 122 so as to contact the sample of body fluid contained in chamber 124. The lower ends of electrodes 126A, 126B and 126C are coated with species selective coatings 128A-128C, respectively. Reference electrode 126D also preferably includes a coating 128D on its lower end. Unlike the coatings 128A-128C, reference coating 128D is not species selective. Coded label 48B is attached to the outer surface of tube 120, and contains a machine-readable code which identifies

each of the wire electrodes 126A-126D and provides calibration factors and lot/serial identification numbers.

It can be seen that sensing device 12B shown in Figure 4B requires still a different type of receptacle from the type required by either disposable sensing device 12A or disposable sensing device 12. In the case of sensing device 12B, wire electrodes 124A-124D have their upper ends extending out of the top end of device 12B. The mating receptacle of analyzer 14, therefore, is of a form which has its connecting socket positioned above rather than below sensing device 12B.

Figure 4C shows an embodiment of the present invention which uses coated pin electrodes rather than coated wire electrodes like those shown in Figures 4A and 4B. In Figure 4C, sensing device 12C includes a circular base 130 which supports four pin electrodes 132A-132D in fixed spaced relationship to one another. The lower ends of pins 132A-132D extend out the bottom of base 130 to connect to the electrical connectors of the receptacle of analyzer 14.

Cylinder 134 is bonded to base 130 to produce a tube having a cavity 136 for receiving and holding the sample of body fluid to be analyzed. The pin heads of pin electrodes 132A-132D are exposed to the sample of body fluid. The pin heads of pin electrodes 132A, 132B and 132C have species selective coatings 138A-138C, respectively, on their upper surfaces. The pin head of reference pin electrode 132D has a reference coating 138D on its upper surface. Coded label 48C is attached to the outer

surface of cylinder 134. The machine-readable code contained in coded label 48C identifies pin electrodes 132A-132D, provides calibration data for each electrode, and provides lot and/or serial number identification of sensing device 12C.

Figure 4D shows still another embodiment of the present invention which uses flat film sensing electrodes and a two-part sensing device assembly. Sensing device 12D includes tube 150 and carrier 152. Tube 150 defines a cavity 154 for receiving and holding a sample of the body fluid to be analyzed. Carrier 152 is inserted into cavity 154, and supports flat film electrodes 156A-156D. In the embodiment shown in Figure 4, flat film electrodes 156A and 156B are vertical electrodes positioned on the back side of carrier 152, while electrodes 156C and 156D are located on the front side of carrier 152. Each sensor electrode 156A-156D is exposed at the upper end of carrier 152 to permit connection to a mating receptacle of analyzer 14. At their lower ends, electrodes 156A-156D include coatings which (in the case of electrodes 156A-156C) selectively interact with predetermined species which are contained in the sample of body fluid. In Figure 4D, coating 158C at the lower end of electrode 156C and reference coating 158D at the lower end of reference electrode 156D are shown.

As in the other embodiments of the present invention, disposable sensing device 12D also includes a coded label 48D which is attached to the outer surface of tube 150. The machine-readable code contained in coded label 160 identifies each of the sensor electrodes 156A-156D, provides calibration

data for those sensing electrodes, and provides lot and/or serial number information.

5. Conclusion

The clinical analyzer system of the present invention provides physicians and other medical personnel with the ability to conduct basic chemistry tests on whole blood and other body fluids without delay and at reasonable cost. The simplicity of the analyzer and disposable sensing device, and the ease of use and lack of maintenance makes the system of the present invention both affordable and convenient for doctors' offices, physician group practices, bedside applications in hospitals, operating and emergency rooms, cardiac and intensive care units, nursing homes, ambulances and emergency vehicles, "stat" use in hospital clinical laboratories, and other applications (such as veternarians' offices and clinics) where clinical chemistry instrumentation has either not been available or has not been cost and time effective.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A clinical chemistry analyzer system for determining a concentration of a selected chemical species in a body fluid, the system comprising:

a single-use sensing device which includes:

a cavity for receiving and holding a sample of the body fluid;

a species selective electrode having a first end exposed to an interior of the cavity and a second end outside of the cavity, the species selective electrode including an electrical conductor which at the first end is covered by and in direct contact with a single layer membrane containing an electroactive species which selectively interacts with the selected chemical species;

a reference electrode separated from the species selective electrode in fixed spaced relationship and having a first end exposed to an interior of the cavity and a second end outside of the cavity;

carrier means for supporting the cavity, the species selective electrode and the reference electrode so that the species selective electrode and the reference electrode contact the sample in the cavity without being in physical contact with one another;

an analyzer which includes:

a receptacle for receiving the single use sensing device, the receptacle including connectors for engagement with the second ends of the species selective electrode and the reference electrode when the single-use sensing device is inserted into the receptacle;

means connected to the connectors for deriving a signal from the species selective electrode and the reference electrode which is a function of concentration of the selected chemical species in the sample; and

means for determining concentration of the selected chemical species in the sample of body fluid based upon the signal.

2. The system of claim 1 wherein the single-use sensing device carries machine-readable indicia which include data for use by the analyzer in determining concentration of the selected chemical species; and wherein the analyzer includes means for reading the indicia.

3. The system of claim 2 wherein the machine-readable indicia include calibration data related to a characteristic of the species sensor for use by the means for determining concentration.

4. A clinical chemistry analyzer system comprising:

a single-use sensing device which includes:

a cavity for receiving and holding a sample of body fluid;

a carrier;

a plurality of sensors supported by the carrier in fixed spaced relationship, each sensor having a sensing portion positioned to be exposed to the sample held within the cavity to produce a sensor signal, the sensing portion of at least one of the sensors being capable of selective interaction with a selected chemical species so that the sensor signal from that sensor is a function of concentration of the selected chemical species in the sample; and

machine-readable indicia containing calibration data associated with the sensors;

an analyzer which includes:

a receptacle for receiving the single-use sensing device;

means for deriving the sensor signals from the the plurality of sensors when the single-use sensing device is received by the receptacle;

means for reading the indicia when the sensing device is received by the receptacle; and

means for providing an output representative of the concentration of the selected chemical species based upon the sensor signals and the calibration data contained in the indicia.

5. A disposable single-use sensing device for use with a clinical chemistry analyzer which determines a concentration of a selected chemical species in a body fluid based upon sensor signals received at a receptacle, the sensing device comprising:

a species selective electrode which interacts selectively with the selected chemical species to cause a predetermined measurable characteristic of the species selective electrode to vary as a function of concentration of the selected chemical species in the sample, the species selective electrode having an electrical conductor covered by and in direct contact with a single layer membrane which contains an electroactive species;

a reference electrode separate from the species selective electrode for contacting the sample, wherein the reference electrode does not interact selectively with the selected chemical species, so that the predetermined measurable characteristic of the reference sensor does not vary in the same manner as in the species sensor;

a cavity for receiving and holding the sample;

a carrier for supporting the cavity and for supporting the species selective electrode and the reference electrode in fixed spaced relationship so that the species selective electrode and the reference electrode contact the sample simultaneously without being directly in contact with one another; and

connection means engageable with the receptacle when the sensing device is in use with the analyzer for connecting the species selective electrode and the reference electrode to the analyzer to permit a sensor signal to be derived which is a function of the predetermined measurable characteristic of the species selective electrode and the reference electrode.

6. The sensing device of claim 5 wherein the carrier defines at least a part of the cavity and supports the species selective electrode and the reference electrode so that they contact the sample within the cavity.

7. The sensing device of claim 5 and further comprising:

a machine-readable indicia associated with the sensing device and containing data uniquely related to the sensing device for use by the analyzer in determining

concentration of the selected chemical species in the sample based upon the sensor signal.

8. A single-use disposable sensing device for use with a clinical chemistry analyzer which determines concentration of a selected chemical species in a body fluid based upon sensor signals, the sensing device comprising:

a cavity for receiving and holding a sample of the body fluid;

a first sensor having a species selective portion located within the cavity which selectively interacts with the selected chemical species to exhibit a predetermined measurable characteristic which varies as a function of concentration of the selected chemical species in the sample and having a portion which extends out of the cavity to provide means for connecting the first sensor to the analyzer when the sensing device is connected to the analyzer;

a second sensor having a portion located within the cavity which does not interact selectively with the selected chemical species to exhibit the predetermined measurable characteristic which does not change with concentration of the selected chemical species in a same manner as the first sensor and having a portion which

extends out of the cavity to provide means for connecting the second sensor to the analyzer when the sensing device is connected to the analyzer; and

machine-readable indicia which include calibration data for use by the analyzer in calculating concentration of the selected chemical species based upon the predetermined measurable characteristic of the first and second sensors.

9. The sensing device of claim 8 and further comprising:

carrier means for supporting the first and second sensors in fixed spaced relationship.

10. The sensing device of claim 9 wherein the carrier means is connected to and defines at least a portion of the cavity.

11. A single-use sensing device for use with a clinical chemistry analyzer, the sensing device comprising:

a cavity for receiving and holding a sample of body fluid;

a carrier;

a plurality of sensors supported by the carrier in fixed spaced relationship so that each sensor has a sensing portion exposed to the sample held in the

cavity to produce a sensor signal, wherein at least one of the sensors is a species sensor having a sensing portion which is capable of selective interaction with a selected chemical species so that the species sensor exhibits a predetermined measurable characteristic which is a function of concentration of that selected chemical species in the sample;

means for providing a connection between the plurality of sensors and the analyzer; and

machine-readable indicia which contain calibration data uniquely related to each species sensor of the plurality of sensors for use by the analyzer in determining concentrations based upon sensor signals derived from the sensors.

12. A clinical chemistry analyzer for use with disposable single-use sensing devices which have a cavity for receiving and holding a sample of body fluid from a patient and a plurality of sensors which interact with selected chemical species in the sample, and which have machine-readable indicia containing calibration data associated with the sensors, the analyzer comprising:

receptacle means for receiving one of the sensing devices and making connection with the sensors of that sensing device;

signal conditioning means connected to the receptacle means for deriving analog electrical sensor signals from the sensing device which are a function of the interaction of the sensors with the sample;

analog-to-digital (A/D) converter means for converting the analog electrical sensor signals to digital sensor signals;

means for reading the indicia when the sensing device is received by the receptacle and providing the calibration data contained in the indicia;

digital computer means for calculating concentration values for the selected chemical species based upon the digital sensor signals and the calibration data; and

output means for providing an output based upon the concentration values.

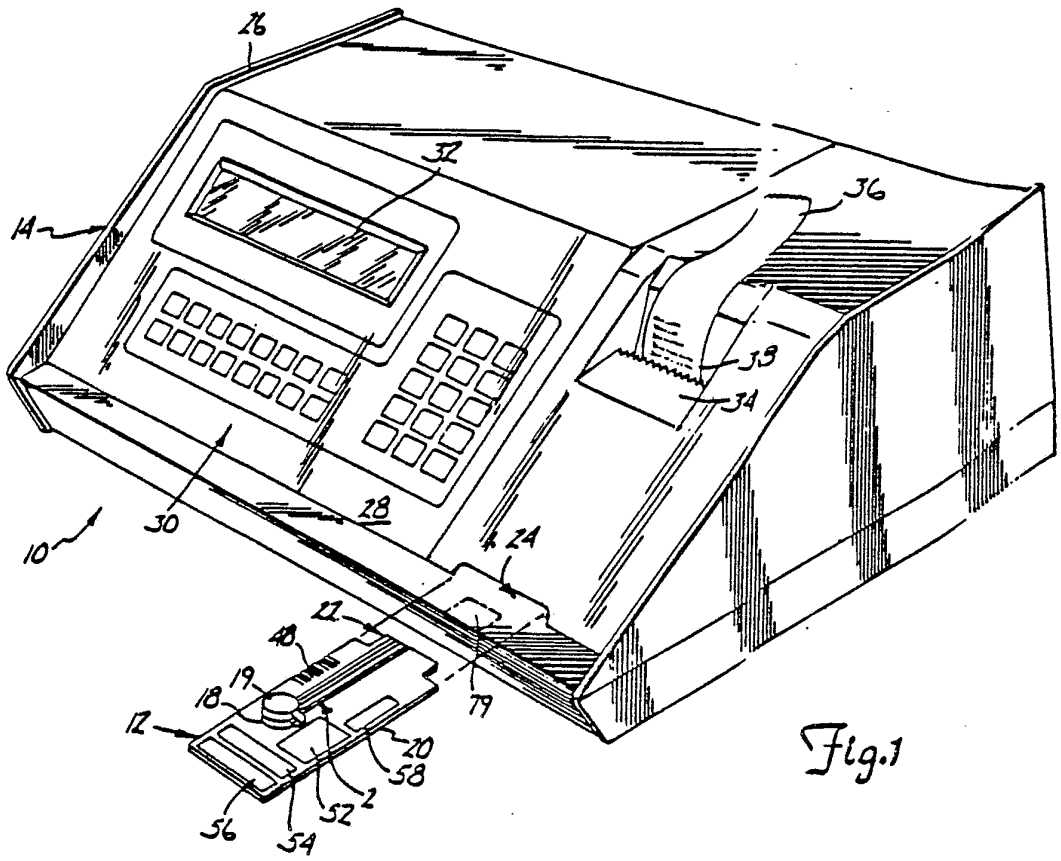

Fig.1

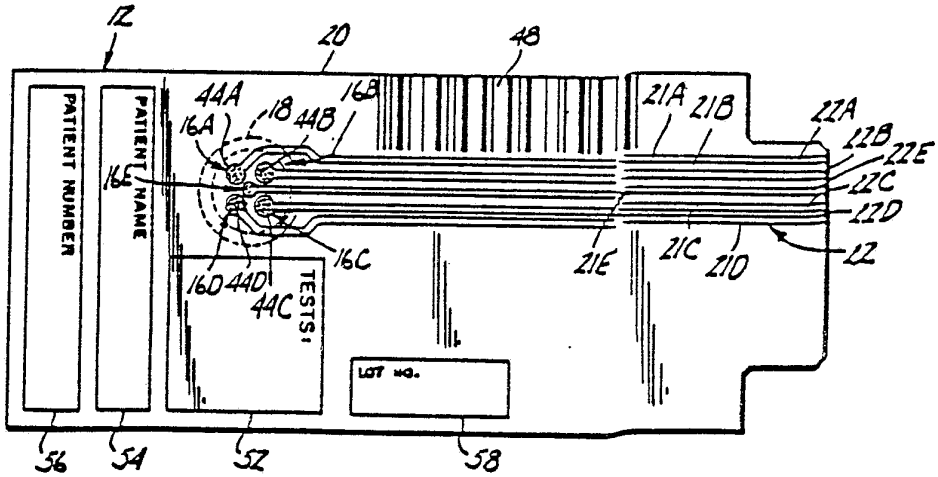

Fig.2

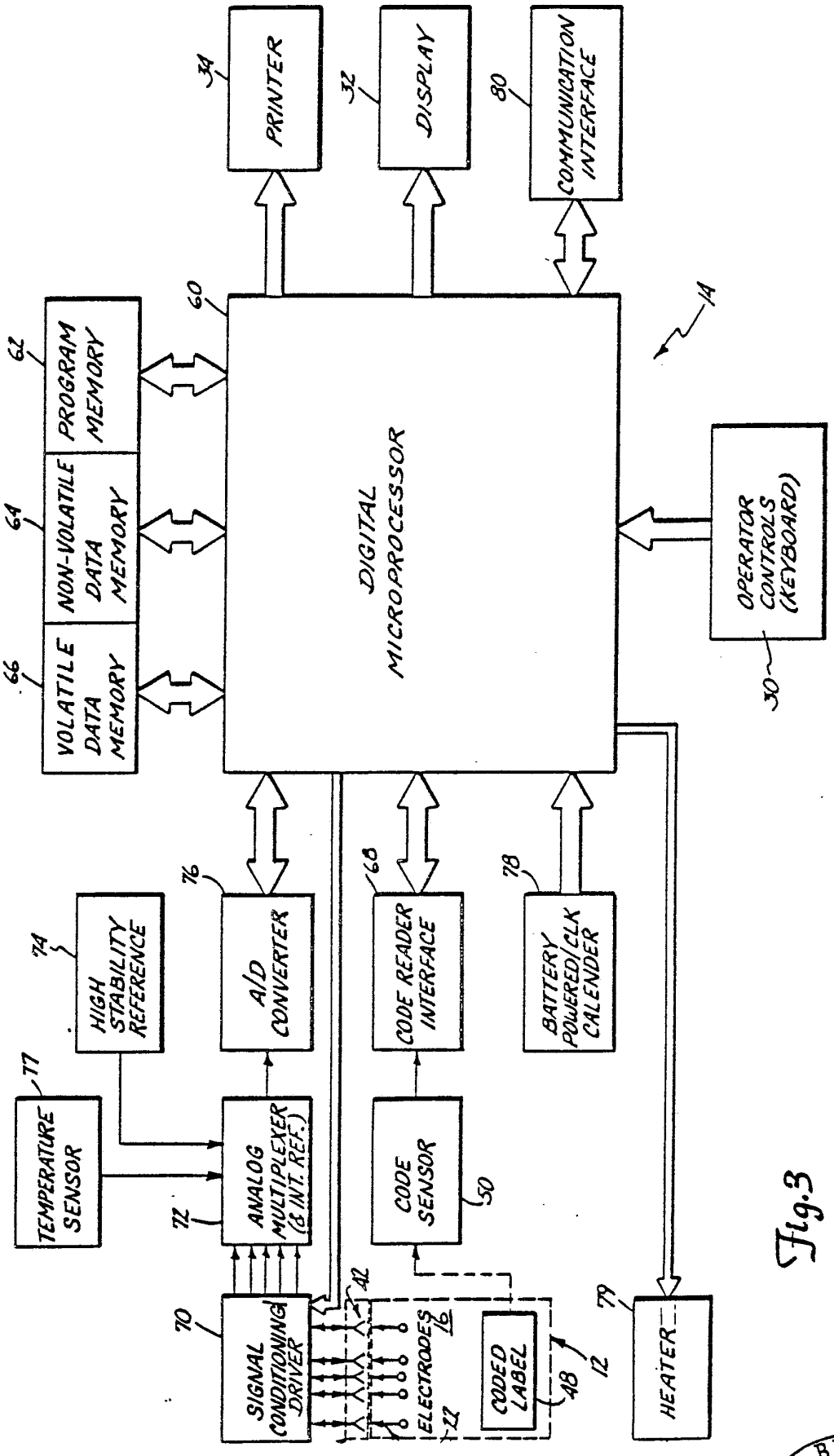

Fig.3

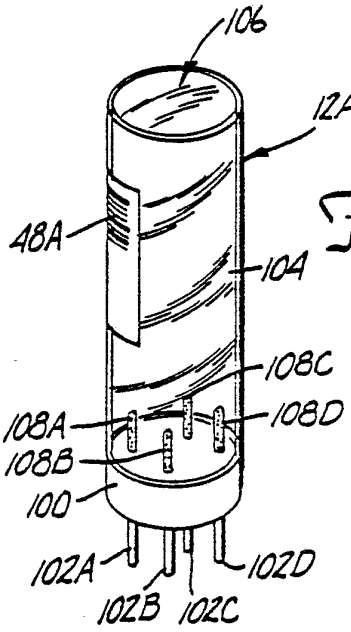

Fig.4A

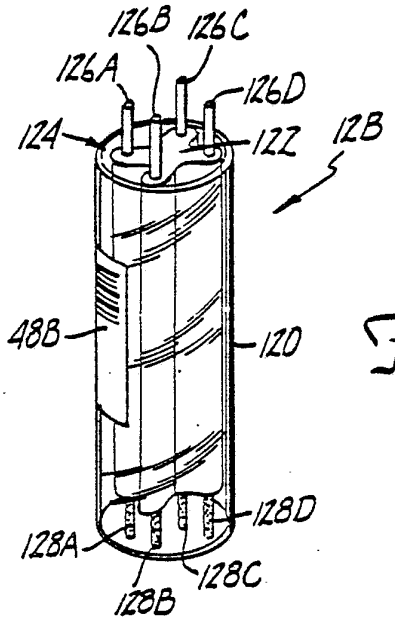

Fig.4B

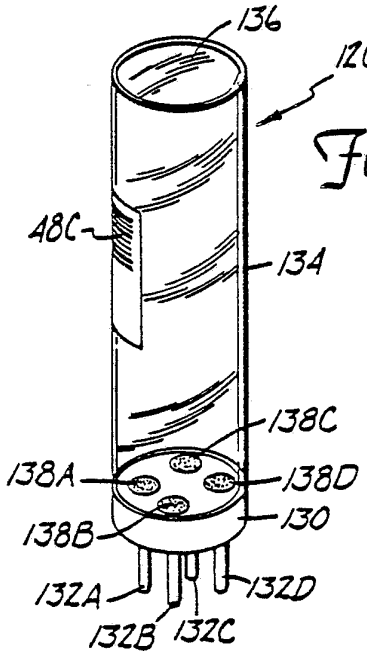

Fig.4C

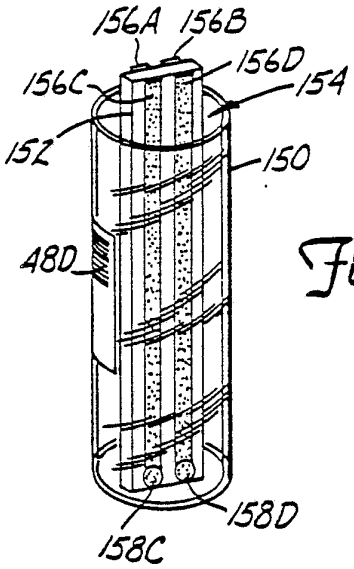

Fig.4D

INTERNATIONAL SEARCH REPORT

International Application No PCT/US84/01814

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL.3 G01N 27/30
U.S. CL. 204/412

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	204/401, 403, 406, 407, 412, 415, 416, 418, 419, 420 204/433; 436/43, 46, 63, 64, 68, 74; 422/68,98,102 435/817; 364/497; 128/635; 204/1T; 73/1R

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	U.S., A, 3,562,129, Published 09 February 1971, Simon	1
A	U.S., A, 3,957,607, Published 18 May 1976, Simon et al	1
A	U.S., A, 4,133,735, Published 09 January 1979, Afromowitz et al	1
A	U.S., A, 4,214,968, Published 29 July 1980, Battaglia et al	1
Y	U.S., A, 4,225,410, Published 30 September 1980, Pace	1-12
Y	U.S., A, 4,250,010, Published 10 February 1981, Kondo et al	1-12
A	U.S., A, 4,340,457, Published 20 July 1982, Kater	1
Y,P	U.S., A, 4,430,299, Published 07 February 1984, Horne, See column 8, lines 51-54	1-12

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
06 December 1984	18 DEC 1984
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	Gerald L. Kaplan GERALD L. KAPLAN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	N, "Clinical Chemistry Testing With The Ames Seralyzer Dry Reagent System", Arthur Karmen et al, The Journal Of Clinical Laboratory Automation, 2982, pages 284-296.	1
Y	N, "Working With Ion-Selective Electrodes", Karl Cammann, pages 121-124, (1979).	1-12
A	N, "The New Kodak Analyzer", "Ektachem 700 Is Here", Clinical Chemistry, July 25, 1983.	1
A	N, "The Urine Systems Analyst", A Brochure From Ames Division, Miles Laboratories.	1

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ....., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
A	N, "Ames Seralyzer System-A Quatitative Solid Phase Blood Chemistry System, A Brochure From Ames Division, Miles Laboratory.	1
A	N, "Ion-Selective Electrodes In Analytical Chemistry", H. Freiser, Editor, pages 173-177 (1978).	1
A	N, "Ion-Selective Electrode Methodology", Arthur K. Covington, Vol. I, pages 155-172, (1979).	1
A	N, "pH Respone Of Platinum And Vitreous Carbon Electrodes Modified By Electropolymerized Films", Graham Cheek et al Analytical Chemistry, Vol. 55, pages 380-381, (1983).	1
A	N, "Poly(Vinyl Chloride) Matrix Membrane Ion-Selective Electrodes", G.J. Moody et al, Ion-Selective Electrodes In Analytical Chemistry, Vol. I, pages 287-308, (1978).	1
A	N, "Ion-Selective Electrodes", E. Pungor et al, pages 259-267, October 1972.	1