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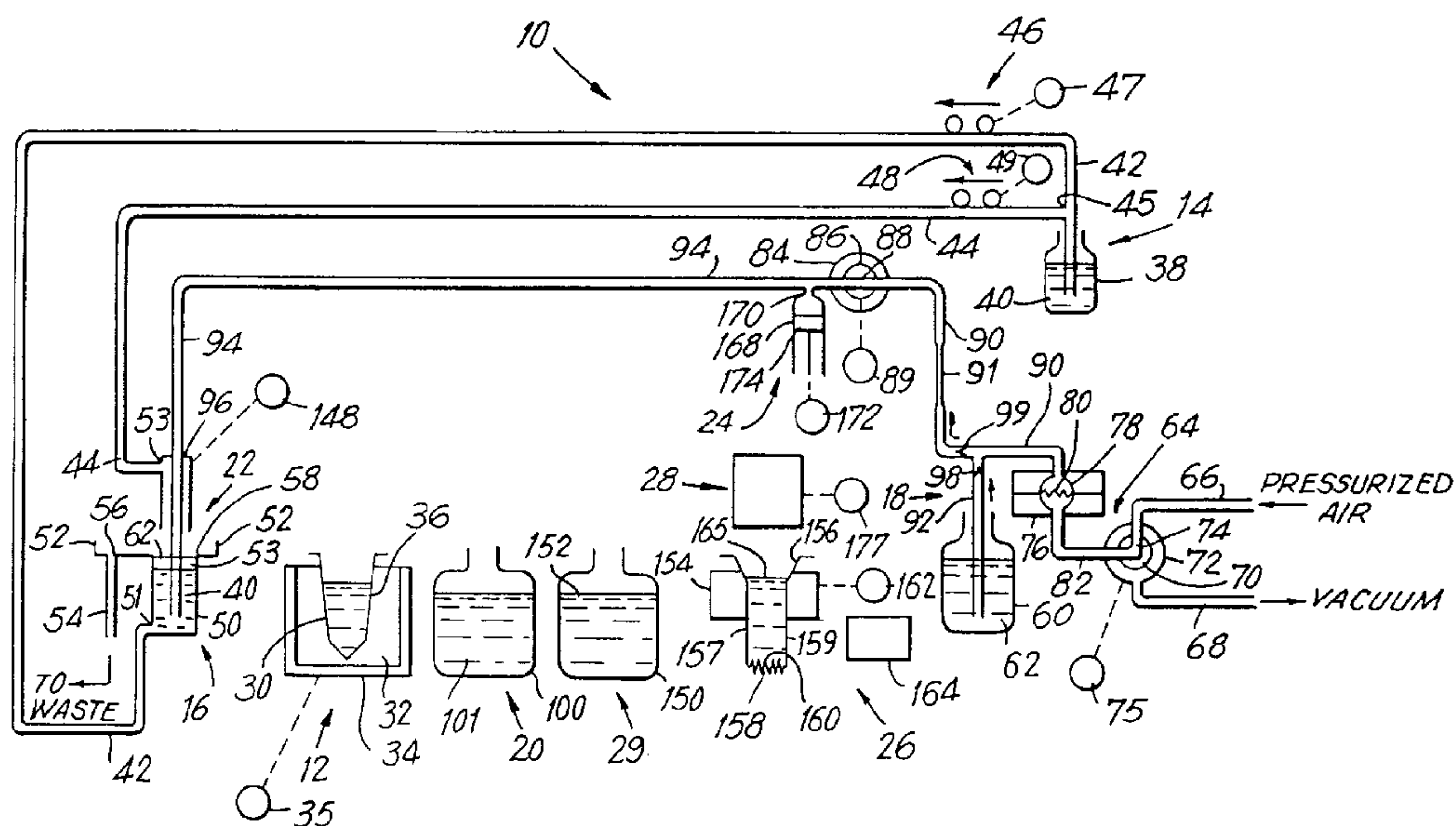
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(54) **ANALYSEUR D'ÉCHANTILLON DE LIQUIDE A FAIBLE EFFET
D'ENTRAÎNEMENT, METHODE ET SYSTEME**

(54) **LOW CARRYOVER SAMPLE LIQUID ANALYSIS SYSTEM AND
METHOD**



(57) The sample liquids analysis system includes a probe which is automatically operable to successively aspirate sample liquids thereinto and to dispense the same into reaction cuvettes for subsequent successive automated sample liquids analyses. Aspiration of a buffer-diluent liquid into the probe for merger therewithin with the sample liquids contributes to sample liquids carryover reduction.

ABSTRACT

5 The sample liquids analysis system includes a probe which is automatically operable to successively aspirate sample liquids thereinto and to dispense the same into reaction cuvettes for subsequent successive automated sample liquids analyses. Aspiration of a buffer-diluent liquid into the probe for merger therewithin with the sample liquids contributes to sample liquids carryover reduction.

LOW CARRYOVER SAMPLE LIQUID ANALYSIS SYSTEM AND METHOD

This application is a divisional application of Canadian application No. 2,019,519, filed June 21, 1990.

5 This invention relates to new and improved apparatus and method for the automated analysis of successive sample liquids with ultra low sample liquid carryover therebetween to maximize the accuracy of the sample liquids analysis results.

Description of the Prior Art

10 Although apparatus and method for the highly effective, automated analysis of successive sample liquids which bear a number of significant similarities to those disclosed herein are disclosed in United States Patent 4,629,703 issued December 16, 1986 to Kenneth F. Uffenhiemer for "Automated Analytical System" and assigned to Technicon Instruments Corporation, Tarrytown, New
15 York, those significant similarities do not include the provision for ultra low carryover between successive sample liquids as made possible by the apparatus and method of this invention.

Although successive sample liquids aspiring and/or dispensing probe means which are highly effective to that task
20 with very low sample liquid carryover are disclosed in United States Patent 4,121,466 issued October 24, 1978 to Allen Reichler et al., for "Liquid Dispenser with an Improved Probe" and assigned to Technicon Instruments Corporation, Tarrytown, it may be understood that the same, which rely solely on an isolation
25 liquid which is immiscible with the sample liquids and which selectively wets the relevant probe walls to the substantial exclusion of the sample liquids to minimize sample liquid carryover, and which specifically rules out the utilization of a

rinse liquid in combination with that isolation liquid to rinse the relevant probe walls, simply cannot provide the ultra low sample liquid carryover as provided by the apparatus and method of this invention. In addition, and although the probe means are only depicted schematically in United States Patent 4,121,466, it is nonetheless clear that the same are totally distinct in structural configuration from those of this invention.

Features of the Invention:

It is a feature of the invention to provide new and improved apparatus and method for the automated analysis of successive sample liquids with ultra low sample liquid carryover therebetween, to thereby maximize the accuracy of the successive sample liquids analysis results.

It is another feature of the invention to provide new and improved successive sample liquids analysis apparatus and method as above which are operable at high sample liquid analyses rates.

It is another feature of the invention to provide new and improved successive sample liquids analysis apparatus and method as above which are immediately applicable, without modification, to a wide variety of different sample liquids analyses with regard to different sample liquids analytes of interest.

It is another feature of the invention to provide new and improved successive sample liquids analysis apparatus as above which are of generally straightforward configuration and manner(s) of operation, and which require the use of only readily available components and materials of proven effectiveness and dependability to the task at hand in the fabrication thereof.

It is a further feature of the invention to provide new and improved successive sample liquids analysis system and method

as above which are particularly, but not exclusively, adapted to the automated performance of non-isotopic immunoassays on human blood sera sample liquids with regard to a broad range of sample liquid analytes, and wherein the ultra low sample liquid carryover provided by the apparatus and method of the invention is a requirement to the accuracy and validity of the immunoassay results.

Summary of the Disclosure

As disclosed herein, the new and improved successive sample liquids analysis system of the invention comprises sample liquid aspirating and dispensing probe means with the improvement comprising, means for aspirating a segment of a buffer-diluent liquid followed by a segment of a sample liquid into the probe means for merger of the buffer-diluent and sample liquid segments in the probe means, and for subsequently dispensing the merged buffer-diluent and sample liquid segments from the probe means, thereby reducing sample liquid carryover upon the aspiration of a segment of a succeeding sample liquid into the probe means.

In its method aspect the invention relates to a method for the analysis of successive sample liquids through use of sample liquid aspirating and dispensing probe means with the improvement comprising the steps of, seriatim, aspirating a segment of a buffer-diluent liquid into the probe means, aspirating a segment of a sample liquid into the probe means for merger of the buffer-diluent and sample liquids segments within the probe means, and dispensing the merged buffer-diluent and sample liquids segments from the probe means, thereby reducing sample liquid carryover upon the aspiration of a segment of a succeeding sample liquid into the probe means.

For use of the sample liquids analysis system in application wherein relatively large volumes of the sample liquids are aspirated and dispensed by the probe means, the invention further includes aspiration of an appropriate

surfactant liquid for mixture with the sample liquids in the probe means; and this functions to better retain the integrity of the sample liquids in the probe means to reduce sample liquid carryover.

5 **Description of the Drawings**

The above and other significant objects and advantages of the invention are believed made clear by the following detailed description thereof taken in conjunction with the accompanying drawings wherein:

10 FIG. 1 is generally schematic view of an automated sample liquids analysis system;

FIG. 2 is a top plan view of the sample liquid aspirating and dispensing probe means of the system of FIG. 1;

15 FIG. 3 is a cross-sectional view taken essentially along line 3-3 in FIG. 2;

FIG. 4 is a schematic diagram of a representative control system for the sample liquids analysis system of FIG. 1; and

20 FIGS. 5, 6, 7 and 8 are respectively cross-sectional views in the nature of FIG. 3 illustrating the respective operational configurations of the sample liquid aspirating and dispensing probe means at various stages in the operation of the sample liquids analysis system of FIG. 1.

Detailed Description of the Invention

25 Referring now to FIG. 1 of the application drawings, an automated, successive sample liquids analysis system is depicted schematically and indicated generally at 10.

The sample liquids analysis system 10 comprises sample

liquid supply means as indicated generally at 12, immiscible
isolation liquid supply and reservoir means as indicated
generally at 14 and 16, respectively, rinse liquid supply means
as indicated generally at 18, buffer-diluent liquid supply means
5 as indicated generally at 20, sample liquid aspirating and
dispensing probe means as indicated generally at 22, sample
liquid pump means as indicated generally at 24, and sample liquid
reaction and analysis means as indicated generally at 26,
respectively. In addition, reagent and/or substrate liquid(s)
10 supply and dispensing means for the addition thereof the sample
liquids in the sample liquid reaction and analysis means for
mixture and reaction therewith as required for sample liquids
analysis, are indicated generally at 28; while supply means for
an agent or agent(s) as may be required in addition to the
15 reagent and/or substrate liquid(s) for sample liquids reaction
and analysis are depicted schematically and indicated generally
at 29 in FIG. 1.

As generally described, it will be readily understood by
those skilled in the automated sample liquids analysis art that
20 the sample liquids analysis system 10 is operable to the
successively supply, react and quantitatively analyze each of a
series of sample liquids in turn with regard to one or more
analytes of interest contained therein; with a major emphasis
regarding system 10 being on the reduction of sample liquid
25 carryover, i.e. the contamination of a succeeding sample liquid
by the residue of a preceding sample liquid, to heretofore
virtually unattainable, ultra low level commensurate with the
exceedingly stringent accuracy requirements of highly
sophisticated and specialized contemporary clinical chemistries,
30 for example those involved in non-isotopic immunoassays on human
blood sera.

As more specifically described, sample liquid means 12

preferably take the general form of those disclosed in each of United States Patents 4,099,921, 4,115,861 and 4,168,955, respectively for "Clinical Analyzer" issued July 11, 1978, November 7, 1978 and September 25, 1979 to Robert W. Allington, and assigned to Instrumentation Specialities Company.

To the above effect, the sample liquids supply means 12 comprise a plurality of like sample liquid receptacles 30, for example seventy-eight receptacles in groups in a plurality of moveable shuttles, one of which is shown at 32 in FIG. 1. The shuttles 32 are in turn supported in and moveable by a shuttle support mechanism as indicated at 34, driven in turn by electric drive motor means as indicated schematically at 35 in FIG. 1; with the mechanism 34 operating to support and periodically move the shuttles 32 in such manner that the sample liquid receptacles 30, each of which contains a quantity of a sample liquid to be analyzed as indicated at 36 in FIG. 1, are indexed in turn to a sample liquid offtake station relative to probe means 22, and retained thereat for precisely the same period of time for the aspiration of precisely the same volume of sample liquid therefrom by the probe means 22 in each instance.

The isolation liquid supply means 14 comprise a container 38 of an appropriate isolation liquid as indicated at 40, and which is immiscible with the sample liquids 36. Readily compressible isolation liquid supply conduits 42 and 44, which branch as indicated at 45, respectively extend as shown in FIG. 1 from container 38 to isolation liquid reservoir means 16 and probe means 22; and pump means, for example peristaltic pumps as schematically indicated at 46 and 48, and which are particularly suitable for precise isolation liquid pumping at low flow rates as discussed in greater detail hereinbelow, are respectively operatively formed as shown with the relevant portions of compressible isolation liquid supply conduits 42 and 44. The

peristaltic pumps 46 and 48 are driven in turn as indicated in FIG. 1 by electric drive motor means as schematically indicated at 47 and 49; and are operable when so driven to supply the isolation liquid 40 in respectively precisely controlled quantities, along those conduits from isolation liquid supply container 38 to isolation liquid inlets 51 and 53 of the isolation liquid reservoir means 16 and probe means 22, respectively.

Although by now believed to be well understood by those skilled in this art, it is here reiterated to insure completeness of this disclosure that for use, for example, with essentially aqueous sample liquids 36, and an active component of probe means 22 of an appropriately hydrophobic material, for example Teflon® as described in detail hereinbelow, the isolation liquid 40 would be constituted, for example, by an appropriately hydrophobic fluorinated or per-fluorinated hydrocarbon liquid, or "oil" as the same has come to be termed in the sample liquids analysis art, which is preferentially attracted to and selectively "wets" that active probe means component to the substantial exclusion of the essentially aqueous sample liquids 36, which are immiscible therewith; thereby substantially preventing the adherence of sample liquid residue to that active probe component. This in turn minimizes sample liquid carryover on the active probe means component, with attendant increase in the accuracy of the sample liquids analysis results. This phenomenon of selective wettability, and the application thereof to sample liquids analysis for minimization of sample liquid carryover through use of an appropriate isolation liquid, is disclosed in some detail in each of United States Patent 4,602,995 issued July 29, 1986 to Michael M. Cassaday, et al, for "Liquid Level Adjusting And Filtering Device," United States Patent 4,515,753 issued May 7,

1985 to John L. Smith, Ph.D, et al, for "Integral Reagent Dispenser", and United States Patent 4,678,641 issued July 7, 1987 to Michael M. Cassaday, et al, for "Isolation Liquid Layer Retention Device", all assigned to Technicon Instruments Corporation of Tarrytown, New York.

The isolation liquid reservoir means 16 comprise an open topped, generally cylindrical reservoir body member 50 fabricated for example from an appropriately hydrophobic plastic material by molding, which is supplied as shown in FIG. 1 at inlet 51 at the bottom of the body member with isolation liquid 40 from container 38 by peristaltic pump 46 via supply conduit 42 as discussed hereinabove. An enlarged liquid overflow chamber 52 is formed as shown at the top of the reservoir body member 50, and comprises a drain conduit 54 extending downwardly therefrom as indicated to waste; it being noted that the level 56 of the upper end of the drain conduit 54 is coincident with the level 58 of the top of the reservoir body member 50, whereby the liquid level in the reservoir means 16 will be maintained coincident therewith, with any excess liquid flowing therefrom to waste via drain conduit 54.

The rinse liquid supply means 18 comprise a container 60 of any suitable rinse liquid, for example distilled water, as indicated at 62 in FIG. 1. Rinse liquid supply pump and pump drive means are indicated generally at 64, and comprise pressurized air and vacuum supply conduits 66 and 68 which respectively extend as shown from non-illustrated sources thereof to the rotatable body member 70 of a three-way valve 72, including valve passage 74. Rotatable valve body member 70 is driven as shown by electric drive motor means, for example a solenoid, as indicated schematically at 75 in FIG. 1.

A diaphragm pump is indicated at 76, and includes a pumping chamber 78 divided as shown by a diaphragm 80; and a conduit 82 extends as shown in FIG. 1 to connect valve passage 74 of valve 72 with one side of pumping chamber 78.

A two-way rinse liquid supply valve is indicated at 84, and includes a rotatable valve body member 86 having a valve passage 88 extending therethrough. Valve body member is driven as shown by electric drive motor means, again for example a solenoid, as indicated at 89. A conduit 90 extends as shown to connect the other side of pumping chamber 78 with one side of rinse supply valve 84. A conduit 92 branches as shown from conduit 90 to extend into the supply of rinse liquid 62 in container 60; while a flexible conduit 94 extends as shown to connect the other side of valve 84 to the rinse liquid inlet 96 of the probe means 22. Check valves as indicated at 98 and 99 are provided in conduits 90 and 92 to restrict rinse liquid flow therein to the indicated directions; while conduit 90 comprises a flow restrictor tube section 91 which restricts rinse liquid flow therethrough to levels which will not degrade the effectiveness of the isolation liquid in minimizing sample liquid carryover in the probe means 22 as discussed in greater detail hereinbelow.

For operation of the rinse liquid supply means 18 to supply rinse liquid 62 from container 60 to the rinse liquid inlet 96 of the probe means 22, and with the body member 86 of two-way valve 84 rotated to the "open" position thereof of FIG. 1 to connect conduits 90 and 94, it will be clear that cycling of the rotatable valve body member 70 of three-way valve 72 between the depicted position thereof wherein valve passage 74 connects conduits 66 and 82, and the non-illustrated position thereof wherein passage 74 connects conduits 68 and 82, respectively, will drive pump diaphragm 80 to pump the rinse liquid 62 from container 60 via conduits 92, 90 and 94 for supply to the rinse liquid inlet 96 of the probe means 22.

The buffer-diluent liquid supply means 20 comprise an open-topped container 100 of the buffer-diluent liquid, for example distilled water, as indicated at 101 in FIG. 1. For certain applications of the analysis system 10 of our

invention, as dictated in part by the volumes of the sample liquids 36 to be aspirated by the probe means 22, the buffer-diluent 101 may include a predetermined quantity by volume, for example 20%, of an appropriate surfactant, for example that readily available under the Trademark "Triton X-100," which operates in conjunction with the isolation liquid 40 and the rinse liquid 62 to even further reduce sample liquids carryover to the requisite ultra low levels as discussed in greater detail hereinbelow.

With reference now to FIGS. 1, 2 and 3 of the application drawings for more detailed description of the probe means 22, the same will be seen to comprise a generally cylindrical body member 102 having a stepped, generally axial bore 103 extending therethrough, and comprising axially aligned bore sections 104, 106 and 108 as best seen in FIG. 3. Bore section 104 is threaded as indicated at 110 almost to the inner end thereof, leaving an unthreaded bore section 111 of relatively small axial extent at that inner bore end.

The active probe component is indicated generally at 112 in FIG. 3, and comprises a generally pipette-like body member 114 having a tubular upper body portion 116 which smoothly transitions or "necks down" as shown at 118 to a lower tubular body portion 120 which extends from the probe body member 102 well below the lower surface 123 thereof to terminate in an open tip 122. This configuration of the probe component 112 of course provides for a greater probe component volume per unit length for upper probe body portion 116 than for lower probe body portion 120; and, for a constant liquid flow rate into the probe component 112 through open tip 122, will in turn provide for a lower liquid flow velocity through the upper probe body portion 116 than through the lower probe body portion 120.

The active probe component 112 is operatively disposed in the body member bore 103 concentrically thereof,

with the outer wall of upper probe component body portion 116 being in firm surface contact with the wall of bore section 106 to prevent radial movement of the probe component 112 relative to probe body member 102; and the probe component 112 extends as shown through body member bore section 108 with wall clearance to provide an annulus as indicated at 121 therebetween to completely surround the relevant wall surfaces of the upper probe component body portion 116 which extends therethrough.

A length of tubing of a material of appropriate strength characteristics is indicated at 125 in FIG. 3, and is disposed as shown, for example by press-fitting, in body member bore portion 108 to extend therefrom and surround upper probe component portion 116, both within annulus 121 and for some distance below the lower surface 123 of probe body member 102, essentially for preventing excessive radial movement of the relevant portion of the active probe component 112 relative to the body member 102, and to provide some measure of protection against impact damage to the same.

A generally radially, downwardly extending stepped bore is indicated at 127 in FIG. 3, and extends as shown through the probe body member 102 into fluid flow communication with the annulus 121; and the end portion of isolation liquid supply conduit 44 extends thereinto as shown, and is retained therein in any appropriate manner, for example by simple press-fitting, to thus place conduit 44 and annulus 121 in isolation liquid flow communication.

A hex nut is indicated at 124 in FIG. 3, and is threaded as shown at 126 for the screwing thereof into the complementally threaded probe body member bore portion 104. The hex nut 124 comprises a stepped bore 128 extending centrally thereof; and it will be clear that upon tightening of the hex nut 124 into the probe body member 102, the bores 128 and 103 will be in alignment as shown. Stepped hex nut bore 128 includes upper and lower portions 130 and 132, with

the former being larger than the latter; and the inner end of the hex nut 124 includes a relatively small unthreaded portion as indicated at 134 in FIG. 3.

For use, for example, with essentially aqueous sample liquids 36 and a hydrophobic isolation liquid 40 as discussed hereinabove, it may be understood that active probe component 112 is preferably fabricated, as by drawings, from an appropriate hydrophobic plastic material, for example essentially rigid Teflon; while, for all applications, probe body member 102 and hex nut 124 are preferably machines from a clear acrylic material, and tubing length 125 cut to an appropriate length from a piece of stainless steel tubing of suitable diameter.

FIG. 3 makes clear that the rinse liquid supply conduit 94 extend through hex nut bore 128, and that the tubing wall is in firm surface contact with the wall of lower hex nut bore portion 132 to prevent radial movement therebetween; with conduit 94 terminating as shown in a flared end 140 within the unthreaded bore section portion 111 of probe member bore section 104. In like manner, upper probe component body portion 116, which is of the same inner and outer diameters as rinse supply conduit 94, also terminates in a flared end 142 in bore section portion 111; with flared ends 140 and 142 of essentially the same diameter.

Assembly of the probe means 22 is readily accomplished by the simple press-fitting of tubular length 125 into probe means body member bore section 108 to the position thereof depicted in FIG. 3; the simple insertion and movement of active probe component 112 into and through the probe body member bore 103 from above the body member 102 until the component 112 comes to rest in the depicted position thereof with the flared component end 142 in firm contact with the lower surface 144 of bore section 104; the simple insertion and movement of rinse liquid supply conduit 94 into and through the hex nut bore 128 from below until

the conduit comes to rest in the depicted position thereof with the flared conduit end 140 in firm contact with the bottom surface 146 of the hex nut 124; and the equally simple insertion and tightening of the hex nut 124 into the threaded body member bore section 104 to very firmly press the flared probe component and rinse supply conduit flared ends 142 and 140 together between opposed bore section and hex nut surfaces 144 and 146 as depicted in FIG. 3 to form an extremely fluid-tight juncture, or pressure fitting therebetween, and place the same in unrestricted fluid flow communication. The end portion of isolation liquid supply conduit 44 is then simply press-fitted into probe body member bore 127 to the position thereof depicted in FIG. 3 to complete the assembly of the probe means 22.

Electromechanically operable probe means drive means, including appropriate electric drive motor means, are indicated schematically at 148 in FIG. 3; and are mechanically connected as indicated by the dashed line to the probe means body member 102, and operable, in manner well understood by those skilled in this art, to index probe means 22 between respective operable positions thereof relative to sample liquid supply means 12, isolation liquid supply means 16, buffer-diluent supply means 20 and, if required, agent(s) supply means 29, attendant the sample liquids analysis process, all as described in greater detail hereinbelow.

In the manner of buffer-diluent liquid supply means 20, the reaction agent(s) supply means 29 comprise an open-topped container 150 of such agent(s) as indicated at 152. For use, for example, of the sample liquids analysis system 10 in the performance of non-isotopic heterogeneous immunoassays on sample liquids 36 as constituted by human blood sera, a representative agent 152 in question would be magnetic particles, or magnetic solid phase, in suspension in an appropriate buffer-diluent liquid as discussed hereinbelow.

The sample liquid reaction and analysis means 26 preferably take the form of those disclosed in United States Patent 4,357,301 issued November 2, 1982 to Michael M. Cassaday, et al, for "Reaction Cuvette," and assigned to Technicon Instruments Corporation, Tarrytown, New York. To that effect, 5 the reaction and analysis means 26 comprise a circular reaction tray as schematically indicated at 154 in FIG. 1 and a circular array of individual, open-topped cup-like containers, or reaction cuvettes, one of which is indicated at 156, supported adjacent 10 the outer periphery thereof, and respectively including exposed, radially aligned transparent cuvette wall sections as indicated at 157 and 159. The reaction tray 154 and cuvettes are fabricated by molding from an appropriately chemically inert plastic material; and each of the reaction cuvettes 156 comprises 15 a bottom surface 158 of a hydrophillic material having a plurality of upwardly extending ridges or projections as indicated at 160 formed thereon, and which function as described in detail in United States Patent 4,357,301 to penetrate a film of the immiscible isolation liquid 40 which encapsulates the 20 sample liquids 36 upon the dispensing thereof into cuvettes 156 by probe means 22 to render the same physically accessible for mixture and reaction(s) as required with sample liquids analysis reagent(s) and/or agent(s) in the cuvettes. The reaction tray 154 indexed by intermittent rotation, which may be sequentially 25 bi-directional, by electromechanical tray drive means, including an electrical stepping motor as indicated schematically indicated at 162 in FIG. 1, to present the reaction cuvettes in turn to respective stations, for the introduction of those liquids to the cuvette, and appropriate reactions therebetween; and finally 30 therefrom to a sample liquids analysis or "read-out" station whereat sample liquids analysis means, for example an operatively associated colorimeter as schematically indicated at 164 in FIG. 1, are operable to automatically analyze the thusly reacted sample liquids, one of which is indicated at 165 FIG. 1, with

regard to the analyte(s) of interest through the transparent
cuvette wall sections 157 and 159. Operation of an automated
sample liquids analysis system through use of sample liquids
reaction and analysis means 26 as described is disclosed in
5 detail in United States Patent 4,629,703.

The sample liquids pump means 24 preferably take the form
of a very precisely operable syringe pump as indicated at 168 in
FIG. 1, and which is connected as shown to rinse liquid supply
conduit 94 by a branch conduit 170. Syringe pump is driven by an
10 electric drive motor as schematically indicated at 172; and it
will be clear that with rinse liquid supply valve rotated to the
non-illustrated "closed" position thereof, downward movement of
the syringe pump piston 174 will be operable to aspirate sample
liquids 36 in very precisely predetermined quantities through the
15 open tip 122 of probe component 112 (FIG. 3) into the probe
component via the reduced pressure created thereby in the rinse
liquid supply conduit 94.

Reagent and/or substrate liquids supply means 28 may take
any form appropriate to the dispensing of the same into the
20 reaction cuvettes 156 at the request(s) dispensing station(s) as
described hereinabove for mixing and reaction with the sample
liquids 36 within the cuvettes 156 as required for sample liquids
analyses. As such, these supply means may, for example, take the
form of appropriately refrigerated trays or other support
25 mechanisms of reagent and substrate liquids containers, for the
reagent liquids for example the integral dispensers as disclosed
in United States Patent 4,515,753, each with operatively
associated dispensing probe means as disclosed in United States
Patent 4,121,466, and respectively operable to dispense and/or
30 substrate liquid(s) therefrom as required into the reaction
cuvettes at the dispensing stations therefor of the reaction tray
154 as described hereinabove. The required electromechanical
drive means for these operations of course include electric drive
motor means as schematically indicated at 177 in FIG. 1.

FIG. 4 schematically depicts a representative control system for the automated sample liquids analysis system 10; and, to that effect, will be seen to include a system controller as indicated at 178 and taking, for example, the form of an appropriately programmable microprocessor device or "computer" as the same are more commonly termed. System controller 178 is electrically connected as indicated by lines 180, 182, 184 and 186 to probe means drive motor 148, sample supply shuttle means drive motor 35, sample reaction tray drive means drive motor 162 and sample syringe pump drive motor 172, respectively; and system controller 178 is further electrically connected as indicated by lines 188, 190, 192 and 194 to rinse liquid control valve drive motor 89, rinse liquid pump control valve drive motor 75, and peristaltic pump drive motors 47 and 49, which may be combined into one drive motor, respectively. In addition, system controller 178 is electrically connected as indicated by line 196 to colorimeter 164, and as indicated by line 198 to reagent and/or substrate liquids supply and dispensing means drive motor(s) 177; and it will thus be immediately clear to those skilled in this art that the respective automated operations and cycle times of the heretofore described components of the sample liquids analysis system 10 can be very precisely determined, coordinated, synchronized and controlled as required by system programmer 178 through the appropriate programming thereof in accordance with the specific requirements and parameters of the analyses to be performed on the sample liquids 36 by the system 10.

Referring again to active probe means component

112 of FIG. 3, and realizing that dimensions may vary in accordance with the requirements of particular sample liquid analysis applications to which the sample liquids analysis system 10 may be put, it may be understood that, for representative system applications wherein volume of sample liquids 36 of 20 ul are to be withdrawn in turn from successively presented sample liquid receptacles 30 by probe means 22 for dispensing in turn into reaction cuvettes 156 of sample liquid reaction and analysis means 26 for successive, automated sample liquids analyses, active probe component 112 could be of approximately 2.6 inches in overall length, with upper probe component body portion 116 being of approximately 2.0 inches in length, and lower probe component body portion 120 being of approximately 0.6 inches in length, as measured in each instance from approximately the middle, of the necked down probe component portion 118. Under these conditions, and with upper probe component body portion 116 being of approximately 0.06 inches in inner diameter, and lower probe component body portion 120 being of approximately 0.02 inches in diameter, volumes of approximately 75 ul and 5 ul will be provided for the upper and lower probe component body portions 116 and 120, respectively. These representative dimensions will, in any event, provide probe means 22 with the capability of effectively and precisely aspirating and dispensing successive sample liquids 36 of volumes ranging from as small as 1 ul to as large as 75 ul, as described in detail hereinbelow, while insuring with regard to the larger of those sample liquid volumes that no sample liquid 36 ever comes into contact with the somewhat irregular, and thus sample liquid carryover intensive in terms of retention of sample liquid residue, juncture between upper probe component body member portion 116 and rinse liquid supply conduit 94.

For a representative sample liquids analysis system application of this nature, and referring now to FIG.

5 of the drawings which depicts the probe means 22 immediately upon the withdrawal thereof from the isolation liquid reservoir means 16 at the completion of a sample liquid aspiration, dispensing and active probe means component cleansing cycle, the active probe component 112 and connected rinse liquid supply conduit 94 will be seen to be substantially filled with rinse liquid 62, supplied thereto from rinse liquid reservoir 60 as described in detail hereinbelow, followed by a segment 200 of the isolation liquid 40 as aspirated by the probe means from the isolation liquid reservoir 50, again as described in detail hereinbelow. In addition, the inner wall of the active probe means component 112 above the isolation liquid segment 200, extending upwardly therein at least to the juncture thereof with the rinse liquid supply conduit 94 if not higher as depicted, is coated with a thin layer 202 of the isolation liquid 40 (shown as of exaggerated thickness in FIG. 5 for purposes of clarity of illustration) which remains therein from previously aspirated isolation liquid 40; while external wall of the probe component body portions 116 and 120 which extend downwardly below the upper end of annulus 121 are also coated with a thin layer 204 of the isolation liquid 40 (again shown as of exaggerated thickness as above) which flows downwardly thereover from the annulus 121 under the force of gravity, also as described in detail hereinbelow.

At this point in the operation of probe means 22, rinse liquid supply valve 84 has been rotated to the "closed" position thereof; and it may be understood that the combination of atmospheric pressure, and capillary action in the probe component body member 114 as a result of liquid surface tension, will be sufficient to retain the rinse liquid 62 and the isolation liquid segment 200 in the probe component body member 114 to prevent the flow thereof from the same under the force of gravity due to the rinse and isolation liquid "head" in the probe component body

member 114 and rinse liquid supply conduit 94, respectively. For operation with sample liquids volumes of 20 ul as discussed hereinabove, it may be understood that a representative volume for isolation liquid segment 200 would be 10 ul.

5 With the probe means 22 removed from the isolation liquid reservoir 50 to expose the open probe tip 122 to the ambient air, and with rinse liquid supply valve 84 remaining closed, it may be understood that sample liquid supply pump 168 is operated by downward movement of pump piston 174 to aspirate a segment 206 of
10 representative volume of 3 ul of ambient air into probe component 112; and this is followed by the indexing of the probe means 22 and the immersion of the open probe tip 122 in the buffer-diluent liquid 101 in container 100, and the continued operation of sample liquid supply pump 168 as described to aspirate a segment
15 208 of the buffer-diluent liquid 101 into the probe component; it being clear that, although immersion of the open probe tip 122 in any liquid for aspiration of necessity includes the immersion of some portion of lower probe component body member portion 120 therein, such immersion is strictly limited to that lower probe
20 component body member portion. A representative volume for buffer-diluent liquid segment 208 is 10 ul.

 Operation of pump 168 is then discontinued, and the probe means 22 indexed to immerse the open probe tip 122 in the sample liquid 36 in the sample liquid receptacle 30 newly indexed by the
25 shuttle means 32 to the probe sample liquid off-take station; whereupon sample liquid supply pump 168 is re-activated as described to aspirate a sample liquid segment 210 of 20 ul volume into the probe component 112 for merger therewithin with the buffer-diluent liquid segment 208, as shown in FIG. 6, followed
30 by discontinuance of the operation of pump 168 and withdrawal of the probe means 22 from the sample liquid receptacle 30.

FIG. 6, which depicts the operational

configuration of the probe means 22 at this point in the operation of sample liquids analysis system 10 makes clear that aspiration as described of the respective air, buffer-diluent liquid and sample liquid segments 206, 208 and 210 will displace much of the previously aspirated isolation liquid segment 200 to the inner walls of the probe component 112, with only thin isolation liquid segments as indicated at 212 and 214 (again shown as of exaggerated thickness) remaining between the rinse liquid 62, the air segment 206, and the merged buffer-diluent and sample liquid segments 208 and 210 to separate the same. FIG. 6 also makes clear that the continued flow of the isolation liquid layer 204 downwardly along the outer wall of the relevant portion of active probe component 112 under the force of gravity as described will, in accordance with the natural flow characteristics of that highly viscous liquid, operate to cover the trailing, insofar as order of aspiration is concerned, edge of the merged buffer-diluent and sample liquids segments 208 and 210 with a thin layer (again of exaggerated thickness) 212 of the isolation liquid, thereby making clear that the merged buffer-diluent and sample liquids segments 208 and 210 effectively encapsulated in the isolation liquid 40.

With the probe means 22 in the operational configuration of FIG. 6, the same is then indexed to the probe dispensing station immediately above the next available reaction cuvette 156 as has been indexed as described to that station by rotation of tray 154; and, with rinse liquid supply valve 84 remaining closed, sample liquid supply pump 168 is operated by upward movement of pump piston 168 to a precisely predetermined extent to pump all of the isolation liquid-encapsulated, merged buffer-diluent and sample liquid segments 208 and 210 from the probe component 112 into the cuvette 156 through open probe tip 122, thereby leaving the probe means 22 essentially in the operational configuration illustrated in FIG. 7 wherein

the probe component 112 is again substantially filled with the rinse liquid 62, with some measure of the isolation liquid 40 remaining at the probe tip 122 as indicated at 214, and the isolation liquid layers 202 and 204 at the respective outer and inner walls of the active probe component 112 remaining intact, both as also made clear by FIG. 7. A representative volume of the isolation liquid dispensed as described by the probe means 22 into the cuvette 156 with the merged buffer-diluent and sample liquid segments 208 and 210 is 2 ul, with much of the isolation liquid remaining in the active probe means component 112 having been further displaced to the inner walls thereof attendant buffer-diluent and sample liquid dispensing therefrom as described.

The addition of the requisite reagent(s) and/or substrate(s) liquids to the thusly dispensed sample liquid 36 in the reaction cuvette 156 by the supply means 28 for those liquids as heretofore described through appropriate indexing of the reaction tray 154, the further treatment of the same as may be required in the reaction cuvette 156, and the analysis of the thusly reacted and treated sample liquids 165 (FIG. 1) by the optical sample liquids analysis means 164 are then automatically accomplished.

Following sample liquid dispensing as described into the reaction cuvette for analysis, probe means 22 are indexed to the position thereof immediately over the isolation liquid reservoir 50 (FIG. 1), and at least that part of the lower probe member body portion 112 which was immersed as heretofore described in the sample liquid container 30 is immersed in the isolation liquid 40 in that reservoir; whereupon rinse liquid supply valve 84 is opened, and rinse liquid supply pump 76 activated to pump the isolation liquid quantity 214 (FIG. 7), the rinse liquid 62 then present in the active probe component 112 and in rinse liquid supply conduit 94, plus an appropriate quantity of the rinse liquid from rinse liquid supply container 62 to

and the probe means component 112 as the case may be out of the open probe component tip 122 into the reservoir 50 against the direction of aspirated sample liquid flow in the active probe component 112. This very effectively backflushes the interior wall of the probe component 112, virtually insuring the removal of all residue of the just-dispensed sample liquid 36 therefrom; with the thusly pumped rinse liquid, which is of lower specific gravity than the isolation liquid, simply flowing from the probe component 112 into the isolation liquid 40 in the reservoir 50, and rinsing to the top of the latter for flow as indicated as the rinse liquid layer 53 atop the isolation liquid 40 from reservoir 50 through overflow chamber 52 to waste via drain conduit 54 as seen in FIG. 1. A representative volume of rinse liquid 40 which is pumped as described from active probe component 112 during this rinsing cycle is 300 ul.

Rinse liquid supply valve 84 is then closed, and sample supply pump 168 activated to aspirate the 10 ul segment 200 of the isolation liquid 40 into the probe component 112 through open probe tip 122 from the isolation liquid reservoir 50; and the probe component 112 then removed from the isolation liquid reservoir 50 to assume the operational configuration thereof of FIG. 5 for repetition of the sample liquid aspiration and dispensing cycle as described; with a further coating of the isolation liquid having been added to the relevant portion of isolation liquid layer 204 at the exterior wall of the active probe component 112 by the immersion thereof in the same in the isolation liquid reservoir 50 as described.

Replenishment of the supply of the isolation liquid 40 in the isolation liquid reservoir 50, and of the supply thereof to probe body member - active probe component annulus 121 (FIG. 3), both to insure that there is always sufficient isolation liquid in the reservoir 50 to enable the aspiration as described by the probe means 22 of the isolation liquid segment 200 prior to buffer-diluent and sample liquids segments aspirations as

described, and to insure the continued presence of the isolation liquid layers 202 and 204 on the respective interior and exterior walls of the active probe means component 112 attendant all operations of the probe means 22, is provided by the periodic operations of peristaltic pumps 46 and 48 to supply the isolation liquid 40 via conduits 42 and 44 as heretofore described. These periodic operations of pumps 46 and 48 may, for example, occur immediately prior to sample liquid aspiration, and immediately following sample liquid dispensing, respectively; and a representative volume of the isolation liquid 40 thusly supplied per sample liquid aspiration and dispensing cycle of the probe means 22 is 20 ul.

For use, for representative example, of the sample liquids analysis system 10 in the automated performance of heterogeneous immunoassays on human blood sera for determination of the presence of the pregnancy hormone Beta HCG therein, and which require the addition of the magnetic particles 152 (FIG. 1) to the sample and reagent liquids in the reaction cuvette, it may be understood that immersion of the active probe means component 112 in the isolation liquid reservoir 50 as heretofore described following dispensing of a sample liquid 36 into a reaction cuvette 156 would, in turn, be followed only by the pumping of the rinse liquid 62 from reservoir 60 through the probe component 112 against the direction of aspirated sample liquids flow to thoroughly back-flush and rinse the same; whereupon the probe means 22 would be removed from the isolation liquid reservoir 50 without the aspiration of the isolation liquid segment 200, thus leaving

the probe means component 112 filled with rinse liquid 62, with rinse liquid supply valve 84 closed. Sample liquid supply pump 168 is then operated to aspirate a segment 218 of ambient air of representative 3 ul volume through the open probe tip 122 into probe component 112; and this is followed by immersion of the probe component 112 as heretofore described into the liquid-suspended magnetic particles 152 in supply container 150 for the aspiration, again through operation of sample liquid supply pump 168, of a segment 220 of the liquid-suspended magnetic particles 152 thereinto in a representative volume of 20 ul. The operational configuration of the probe means 22 at this stage in the sample liquids analysis process is depicted in FIG. 8.

Following the above, the probe means 22 are indexed to immerse the probe component 122 in a previously dispensed sample liquid 36 in a reaction cuvette 156 to which the requisite reagent liquid(s) have already been added as indicated at 165 in FIG. 1, and the sample liquid supply pump 168 again operated to dispense the liquid suspended magnetic particles segment 220 thereinto for mixture with the appropriately reacted sample liquid; and it will be readily understood by those skilled in this art that, in order to insure that the sample-reagent(s) liquids reaction has proceeded as required to completion in the cuvette 156 of interest prior to the introduction of the liquid-suspended magnetic particles segment 200 thereto, a not insubstantial time period, for representative example 20 minutes, may have elapsed between the time that the sample and reagent(s) liquids were introduced to the reaction cuvette 156, and the time at which the liquid-suspended magnetic particles segment 220 is introduced thereinto. In accordance with the teachings of the invention, the probe means 22 and the sample liquids reaction and analysis means 26 do not remain idle during this time period; but rather, and in accordance with the full random access capabilities

of the sample liquids analysis system 10 as set forth in some detail in United States Patent 4,629,703, remain operational at full capacity to aspirate, dispense, react, treat and analyze other and different sample liquids as heretofore described.

5 Following liquid-suspended magnetic particles dispensing as described, the now again rinse liquid-filled probe means 22 are indexed from the reaction cuvette 156 of interest and returned for immersion of the probe means component 122 to the isolation liquid reservoir 50 for repetition of the probe means
10 rinse cycle as heretofore described, and the withdrawal of the probe component 122 therefrom, either with or without the isolation liquid segment 200 of FIG. 5 depending upon the next application to which the probe means 22 are to be put, namely sample liquid or liquid-suspended magnetic particles aspiration.

15 Although the number of sample liquids analyses that can be accomplished by the sample liquids analysis system 10 can vary in accordance with the particular requirements of the same, a representative operational rate for the system 10 is 120 of such sample liquids analyses per hour; with a representative cycle
20 time for the probe means 22 between successive sample liquids aspirations being approximately 3 seconds.

 In addition to the significant advantages with regard to reduction of sample liquid carryover provided as heretofore described by the isolation liquid layers 204 and 202 on the
25 exterior and interior walls of the active probe means component 112, which advantages are by now well known and understood by those skilled in this art, it will be clear that the sample liquids analysis system 10 of the invention provides the additionally significant advantages, again with regard to
30 reduction of sample liquid carryover, of very thorough rinse of the same; it having been determined that, under certain sample liquids analysis conditions, sample liquids residues, for example in the form of protein molecules as present in human blood sera, which are extremely "sticky", can and do adhere to the isolation

liquid layers at the exterior and interior walls (primarily the latter) of the active probe component; and, that in the absence of rinse thereof, can and do contribute to measurable sample liquid carryover, albeit at very low levels. Forceful rinsing as described of the isolation liquid layer 202 at the interior wall of the active probe component 112 by the rinse liquid in the direction opposite to the direction of aspirated sample liquid flow to back-flush the same has proven effective to remove virtually all of any such sample liquid residue as may be present thereon; while the forceful immersion of the relevant portion of the active probe means component 112 into and through the rinse liquid layer 55 (FIG. 1) and isolation liquid 40 in the isolation liquid reservoir 50, and the subsequent forceful withdrawal of that probe means component portion therethrough following rinse liquid flow as described, have proven effective to remove virtually all of any such sample liquid residue as may be present on the isolation liquid layer 204 on the exterior wall of that relevant probe means component. Too, the virtually constant presence of the rinse liquid 40 in the active probe means component 112, both prior and subsequent to sample liquid aspiration and dispensing as described, of course tends to further cleanse the isolation liquid layer 202 at the relevant interior probe component wall portion by picking up sample liquid residue, if any, therefrom for expulsion from the probe component 112 with the rinse liquid into the isolation liquid reservoir 50 during the probe component rinse cycle.

Additional minimization of sample liquid carryover is provided in the sample liquids analysis system 10 by the aspiration of the buffer-diluent liquid segment 208 which, for the aspiration of sample liquid segments 210 of volume warranting the same, for example 10 ul or above, contains a

reasonably high concentration, for example 20% by volume, of an appropriate surfactant as heretofore described; it being understood that the thusly constituted buffer-diluent liquids segment 208, which merges as heretofore described with regard to FIG. 6 with the subsequently aspirated sample liquid segment 210 to place the highest buffer-diluent liquid concentration at the back or upper end of the thusly merged liquids segment, operates to very significantly reduce the overall surface tension of that merged liquids segment, in particular at the more critical back or upper end thereof, thereby better retaining the physical integrity thereof and providing a far more cohesive merged essentially aqueous liquids segment 208 and 210 in the adjacent presence of the isolation liquid 40 for expulsion as such, essentially without merged liquids segment break-up and attendant "loose" sample liquid residue, from the active probe means component 112 upon segment dispensing as heretofore described into a reaction cuvette 156. In addition, the presence of the surfactant in the buffer-diluent liquid segment 208 functions to materially increase the mobility of the ordinarily not particularly mobile protein molecules as may be present in the sample liquid segment 210, and this greatly reduces the non-specific binding characteristics of those protein molecules, and the likelihood of the same adhering to the isolation liquid layer 202.

In accordance with all of the above, and for use for example in the automated performance of heterogeneous immunoassays on human blood sera samples with regard to the pregnancy hormone Beta HCG as discussed hereinabove, it may be understood that the sample liquids analysis system 10 of the invention has proven effective in tests to date to consistently meet, or even exceed, the ultra low sample liquid carryover limit of 5 parts per million of succeeding sample liquid as required for the validity of the same; and it will be immediately clear to those skilled in this art

that no known automated sample liquids analysis system which relies on isolation liquid alone for sample liquid carryover minimization can consistently meet that particularly stringent standard.

With regard to the probe means 22 of the invention, per se, the same will immediately be seen to also offer the particularly significant advantage of providing for the simple, low cost, and virtually immediate replacement of the active probe means component 112 in the event of physical damage thereto as does occasionally occur due, for example to operator error in the operation of an automated sample liquids analysis system, with minimal analysis system down-time, and virtually no adverse effect upon the requisite fine degree of system calibration, and/or the accuracy of subsequent system operation. More specifically, and in the event of damage to active probe means component 112 requiring the replacement thereof, the system 10 is shut down, hex nut 124 is simply unscrewed and removed from probe means body member 102 without adverse effect of any nature upon rinse liquid supply conduit 94 which simply remains inserted therein as heretofore shown and described, the damaged active probe means component 112 simply removed from probe means body member 102 by pushing the same upwardly from the component bottom until the flared component end 142 can be freely grasped by the fingers or appropriate tool within the probe body member bore 104 for simple removal of the component 112 therefrom, a "new" probe means component 112 simply inserted from the top into the body member bore 103 and pushed therethrough until the flared component end 142 comes to rest on bore surface 144, and the hex nut 124, with the rinse liquid supply conduit 94 remaining operatively disposed therein, and absolutely unchanged with regard to length, configuration, and particular liquid flow characteristics, simply re-inserted into body member bore 104 and screwed tightly thereinto to re-establish the fluid-tight connection between the flared

ends 140 and 142 of the rinse liquid supply conduit 94 and the "new" active probe means component 112, and the requisite communication between the same. This makes clear that replacement of the active probe means component 112 can be readily and conveniently accomplished as described totally without adverse effect upon what is generally termed the "service loop", i.e. the relevant lengths of rinse liquid supply conduit 94, and isolation liquid supply conduit 44, and thus upon the accuracy of subsequent analysis system performance; with the cost of such replacement beyond time costs being limited to the cost of the "new" active probe means component 112 which is, of course, decidedly minimal, and no time-consuming fine recalibration of the sample liquids analysis system 10 required. In accordance with the above, it should be immediately clear to those skilled in this art that no prior art probe means suitable for use in highly sophisticated automated sample liquids analysis systems of the type here under discussion can meet these highly demanding requirements of ease, low cost, minimal system down-time and virtually non-existent adverse impact upon subsequent system performance with regard to effective probe means replacement.

Various changes can of course be made in the invention as disclosed herein without departing from the spirit and scope thereof as defined in the appended claims.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. In a sample liquids analysis system for the analysis of successive sample liquids comprising sample liquid
5 aspirating and dispensing probe means, the improvements comprising, means for aspirating a segment of a buffer-diluent liquid followed by a segment of a sample liquid into said probe means for merger of said buffer-diluent and sample liquid segments in said probe means, and for subsequently
10 dispensing said merged buffer-diluent and sample liquid segments from said probe means, thereby reducing sample liquid carryover upon the aspiration of a segment of a succeeding sample liquid into said probe means.

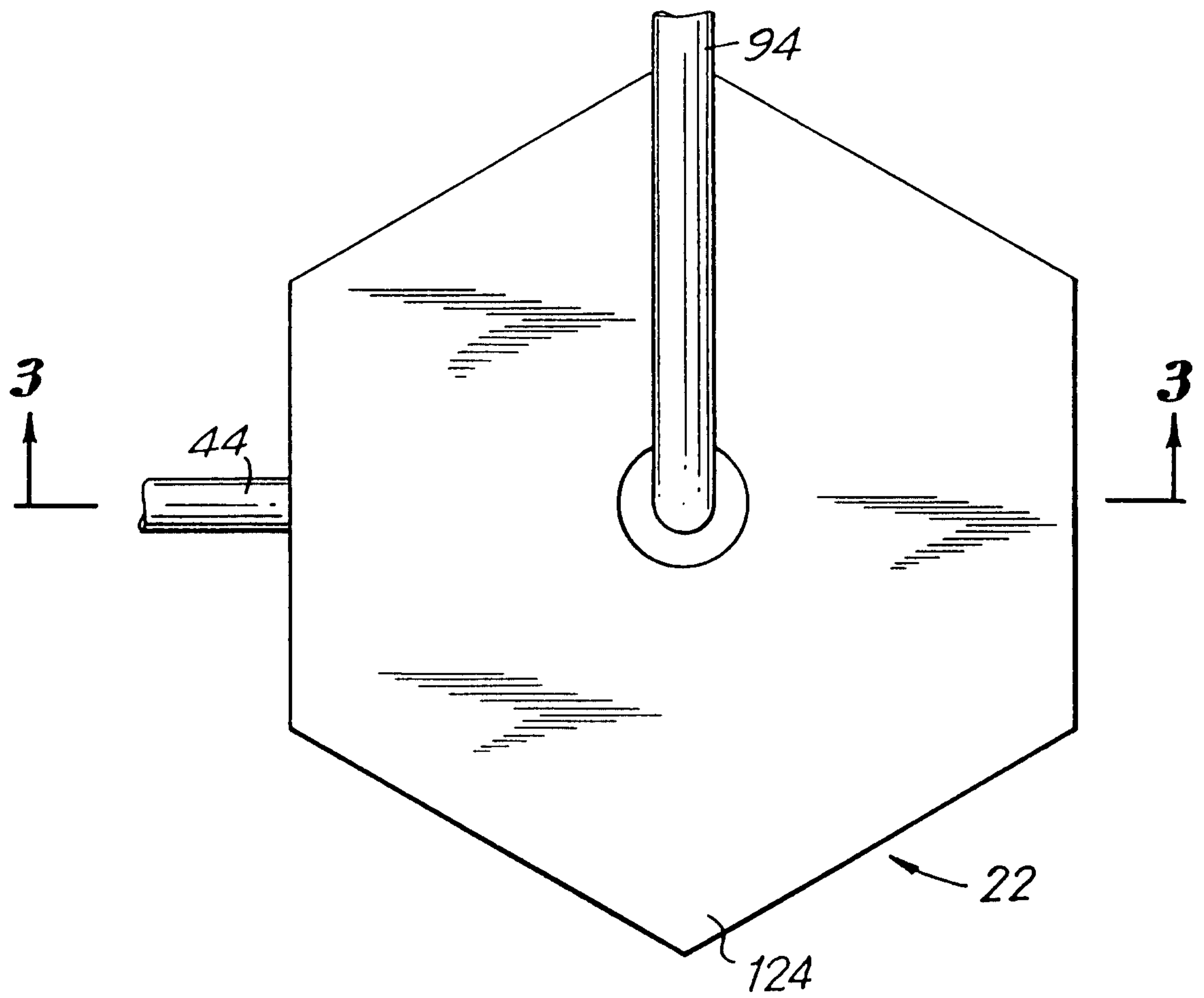
2. In a sample liquids analysis system as in claim 1
15 wherein, said buffer-diluent and sample liquids are essentially aqueous, the improvements further comprising, said buffer-diluent liquid including a surfactant, thereby further reducing sample liquid carryover.

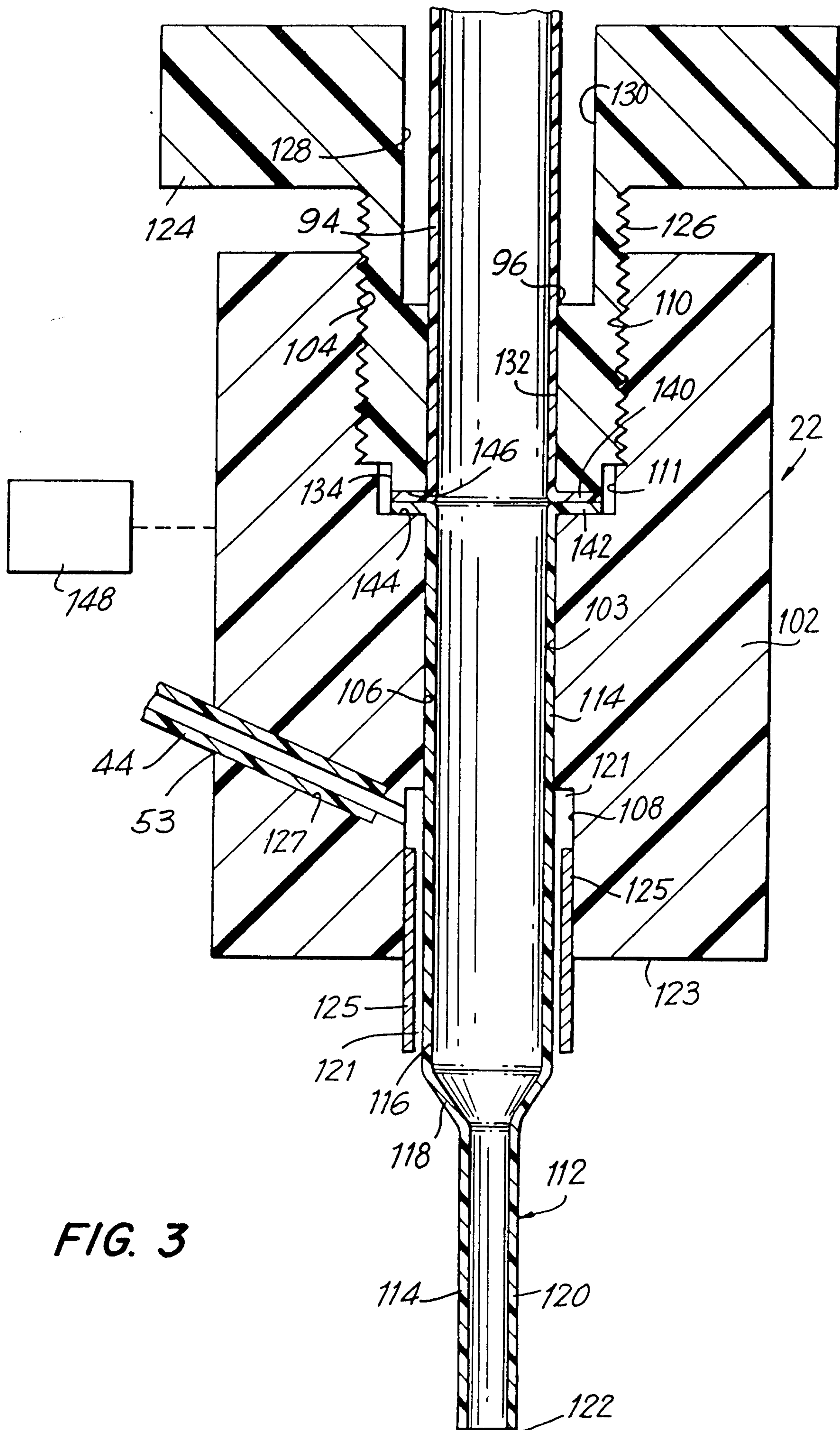
3. In a method for the analysis of successive sample
20 liquids through use of sample liquid aspirating and dispensing probe means, the improvements comprising, the steps of, seriatim, aspirating a segment of a buffer-diluent liquid into said probe means, aspirating a segment of a sample liquid into said probe means for merger of said buffer-diluent and sample
25 liquids segments within said probe means, and dispensing said merged buffer-diluent and sample liquids segments from said probe means, thereby reducing sample liquid carryover upon the aspiration of a segment of a succeeding sample liquid into said probe means.

30 4. In a method as in claim 3 wherein, said buffer-diluent and sample liquids are essentially aqueous, the improvements further comprising, the steps of, adding a

surfactant to said buffer-diluent liquid, thereby further reducing sample liquid carryover in said probe means.

FIG. 2





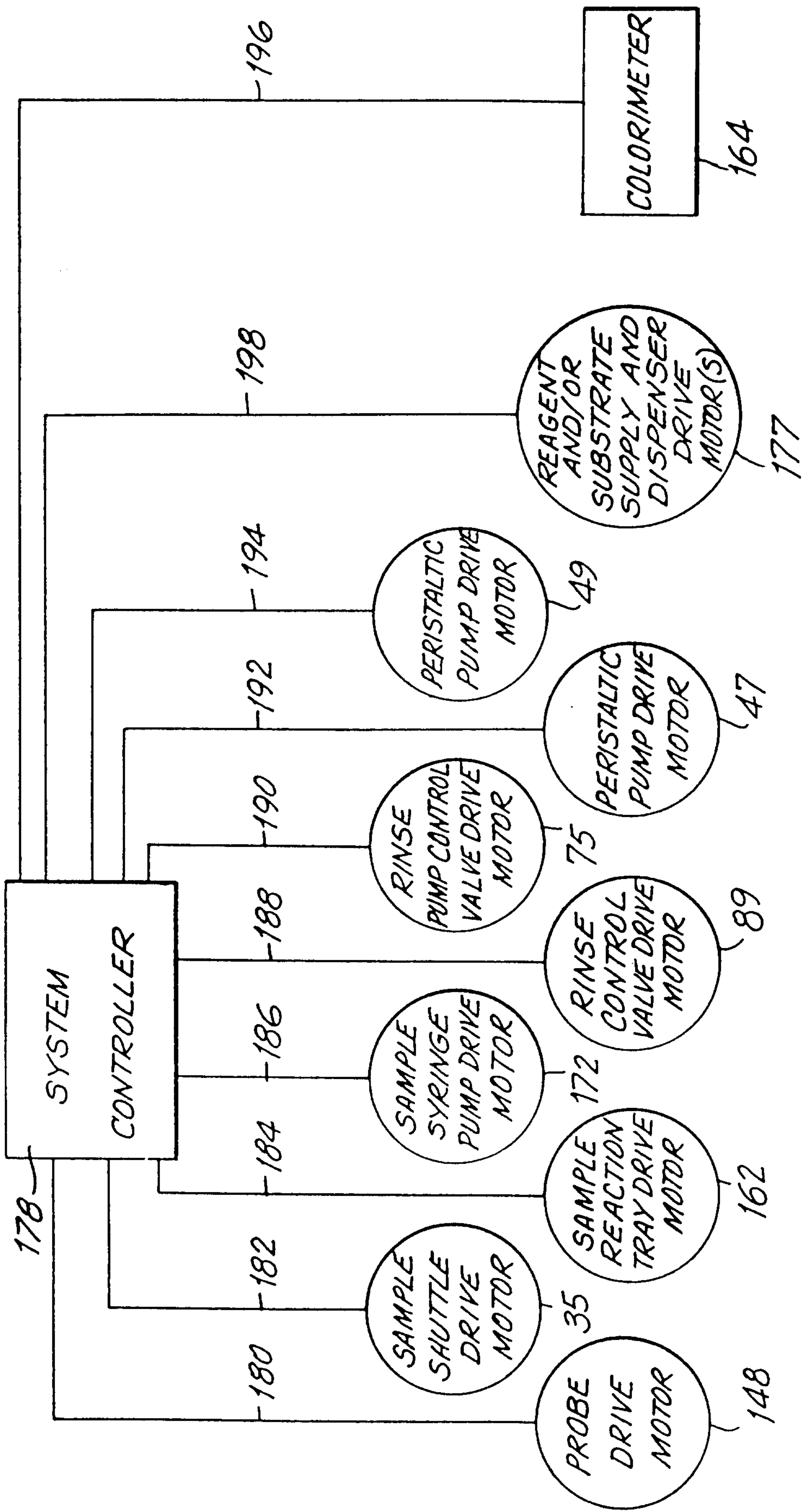


FIG. 4

FIG. 5

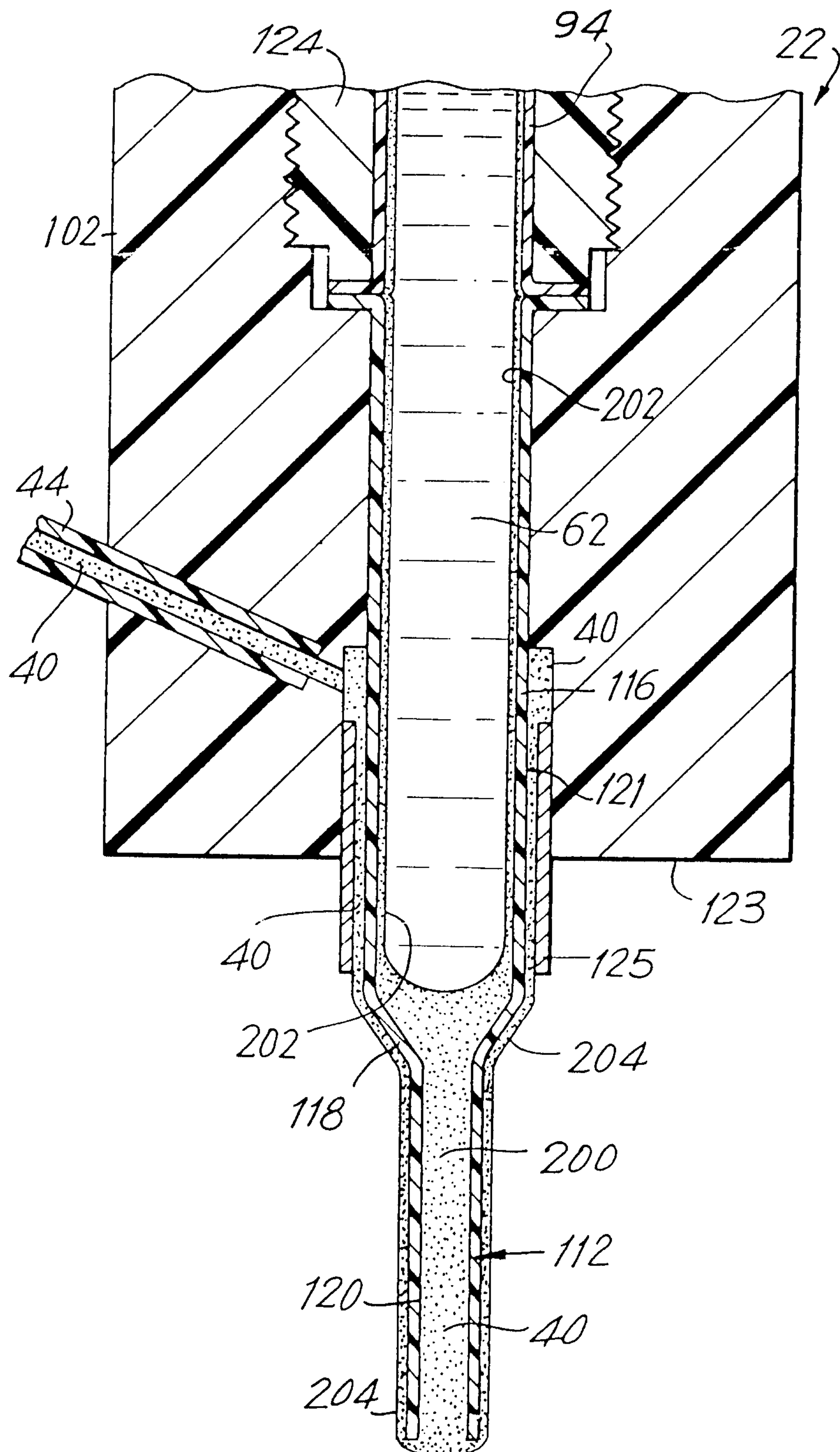


FIG. 6

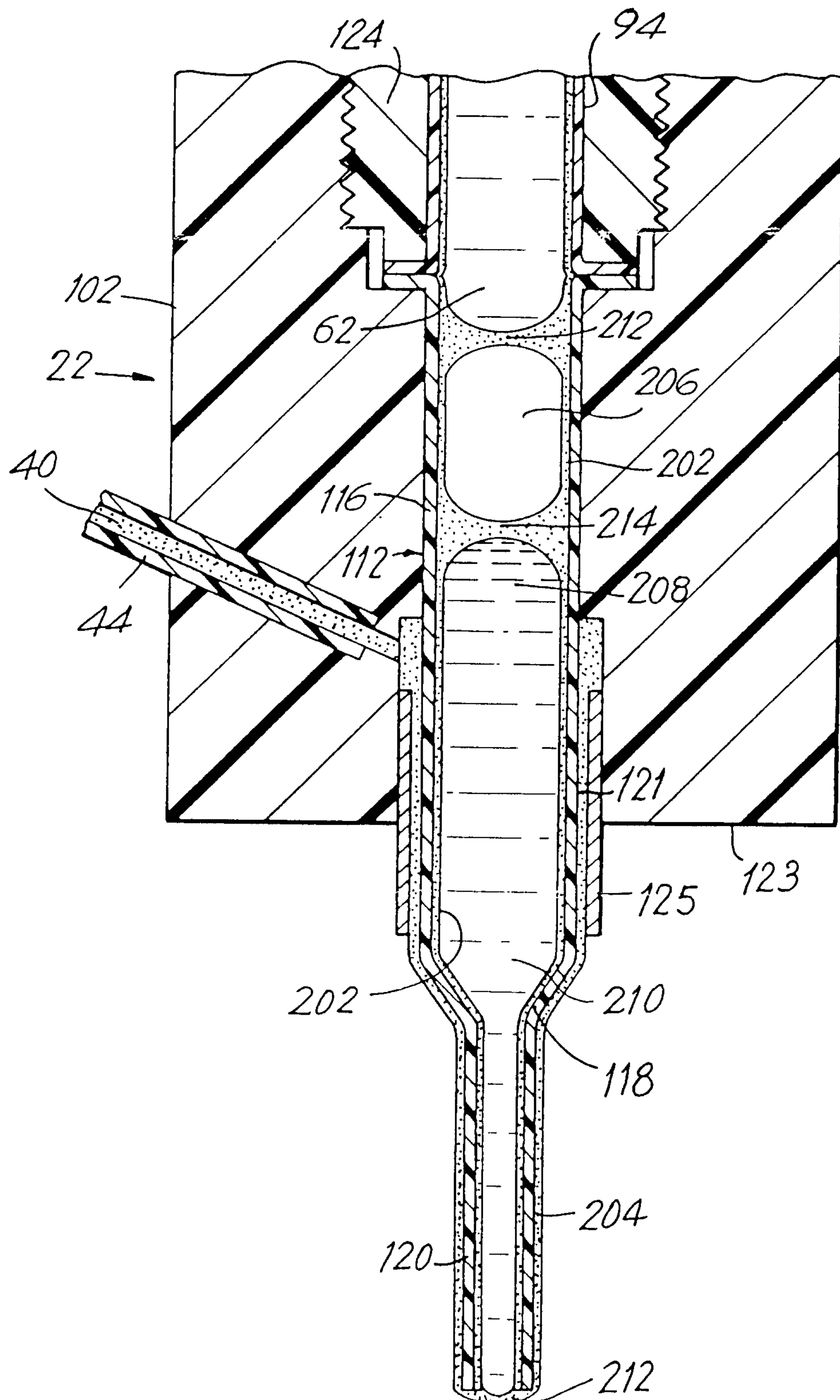


FIG. 7

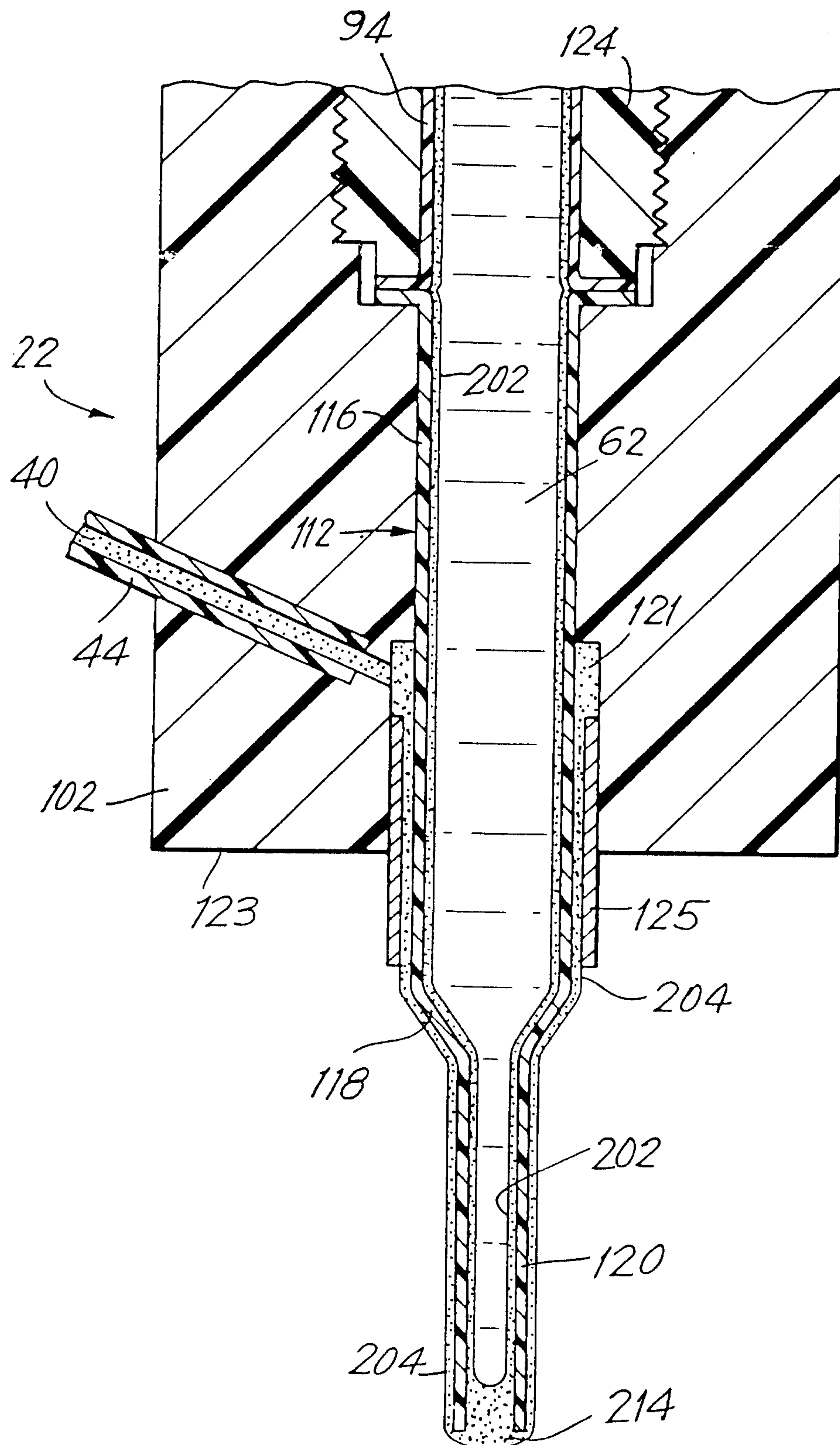


FIG. 8