United States Patent

Thiers

[15] 3,719,087

[45] Mar. 6, 1973

[54] **PIPETTING APPARATUS AND METHOD**

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[73] Assignee: **Bio-Science Laboratories**, Van Nuys, Calif.

[22] Filed: **July 23, 1970**

[21] Appl. No.: **57,720**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 860,775, Sept. 24, 1969, Pat. No. 3,607,082, Continuation-in-part of Ser. No. 541,306, April 8, 1966, Pat. No. 3,475,128.

[52] **U.S. Cl.**.....**73/425.6**, 141/26

[51] **Int. Cl.**.....**B01l 3/02**

[58] **Field of Search**.....73/425.4 P, 425.6; 23/292 R, 23/259 R; 141/18, 25, 26, 27, 28

[56] **References Cited**

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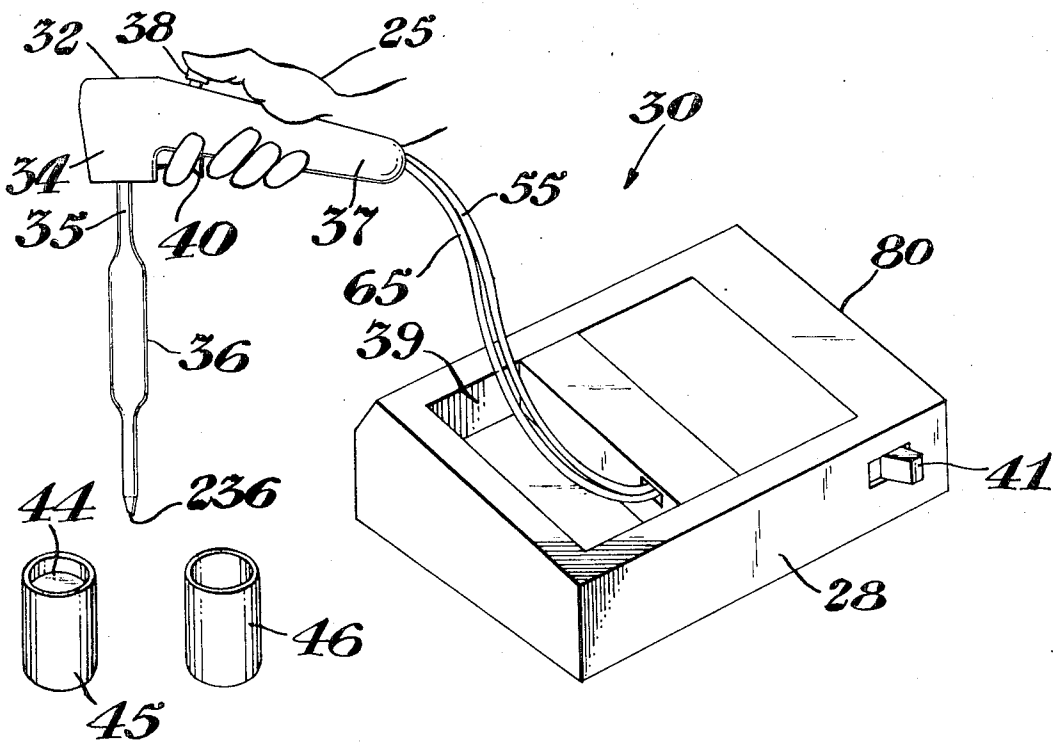
Primary Examiner—S. Clement Swisher

Attorney—Griswold and Burdick, C. Kenneth Bjork and Maynard R. Johnson

[57] **ABSTRACT**

An automatic pipetting apparatus comprises a hand-holdable pipet-operating apparatus which includes means for releasably coupling a plurality of interchangeable pipets to a low-dead-space valving structure. The valving structure operates the pipets by selectively sealing or applying suction or pressure to a pipet. A pipet driving subassembly including pressure and suction pumps is coupled to the pipetting apparatus by flexible tubes, permitting continuous application of suction and pressure to the pipet-operating apparatus as well as free movement of the pipet-operating apparatus with respect to the pipet driving subassembly.

29 Claims, 23 Drawing Figures



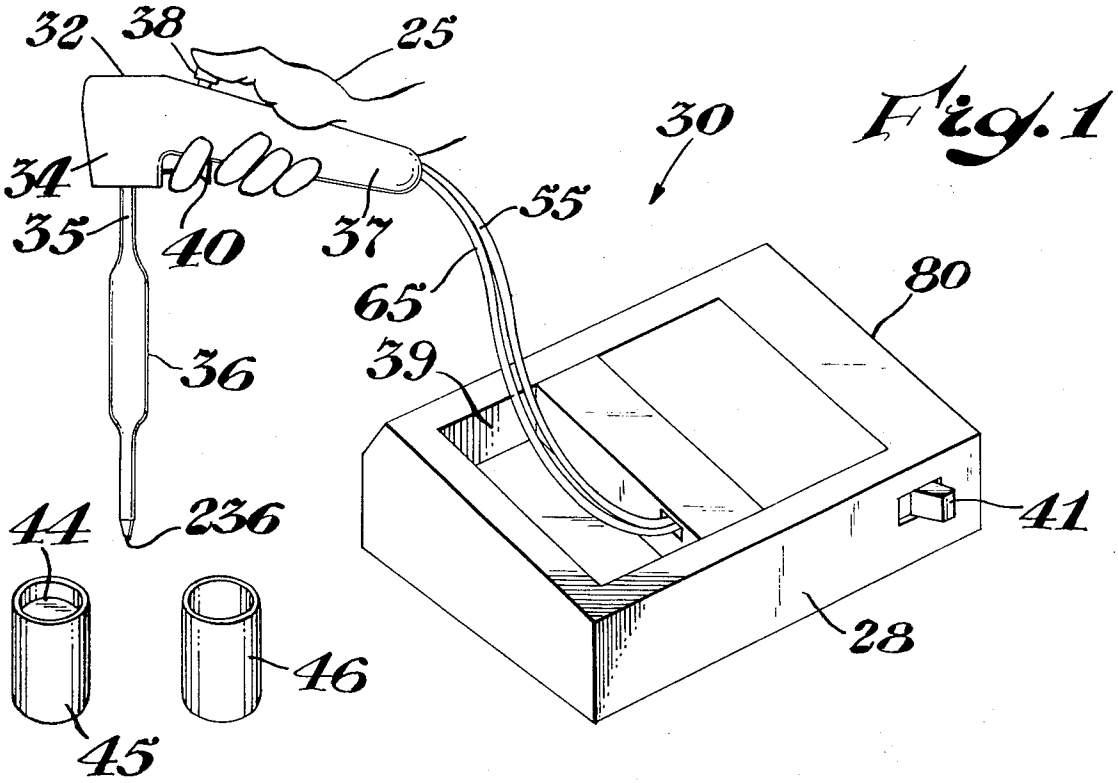


Fig. 1

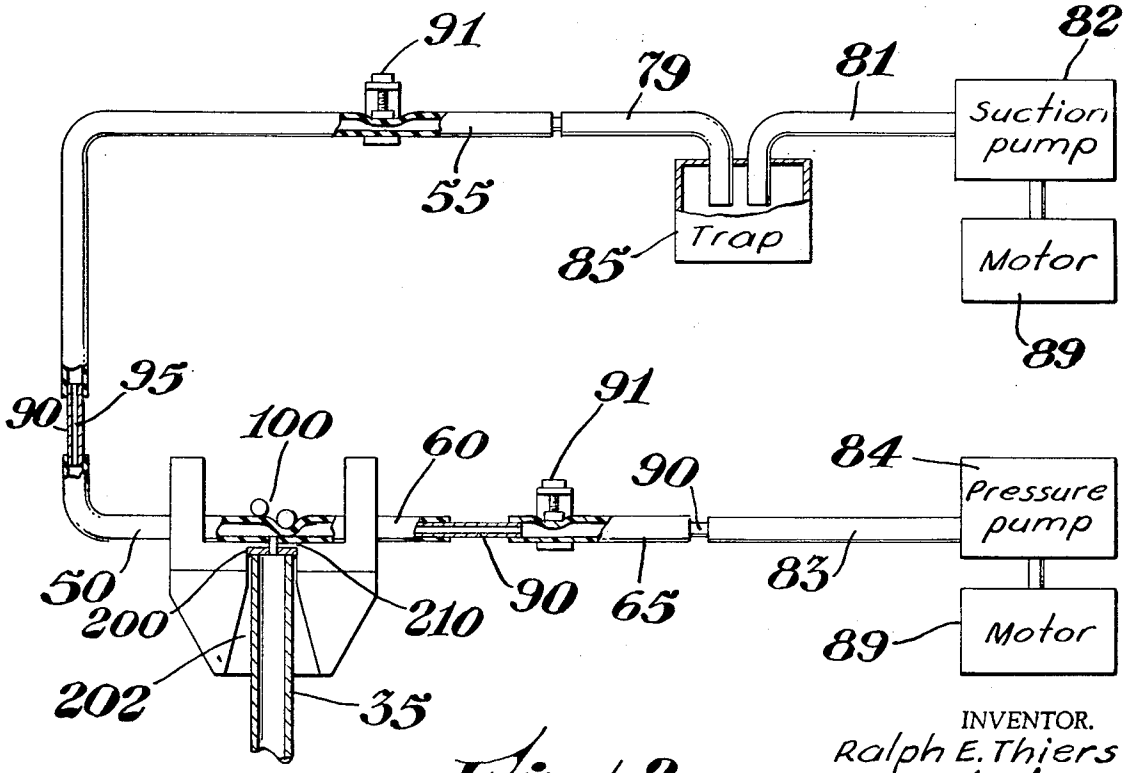


Fig. 2

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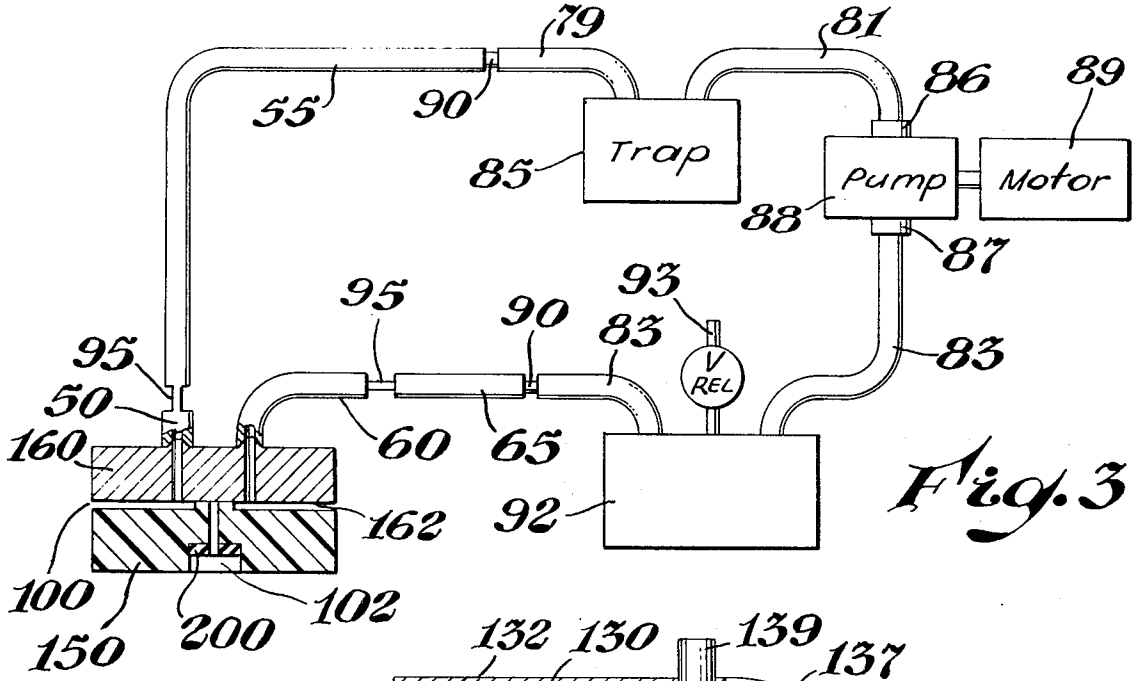

Fig. 3

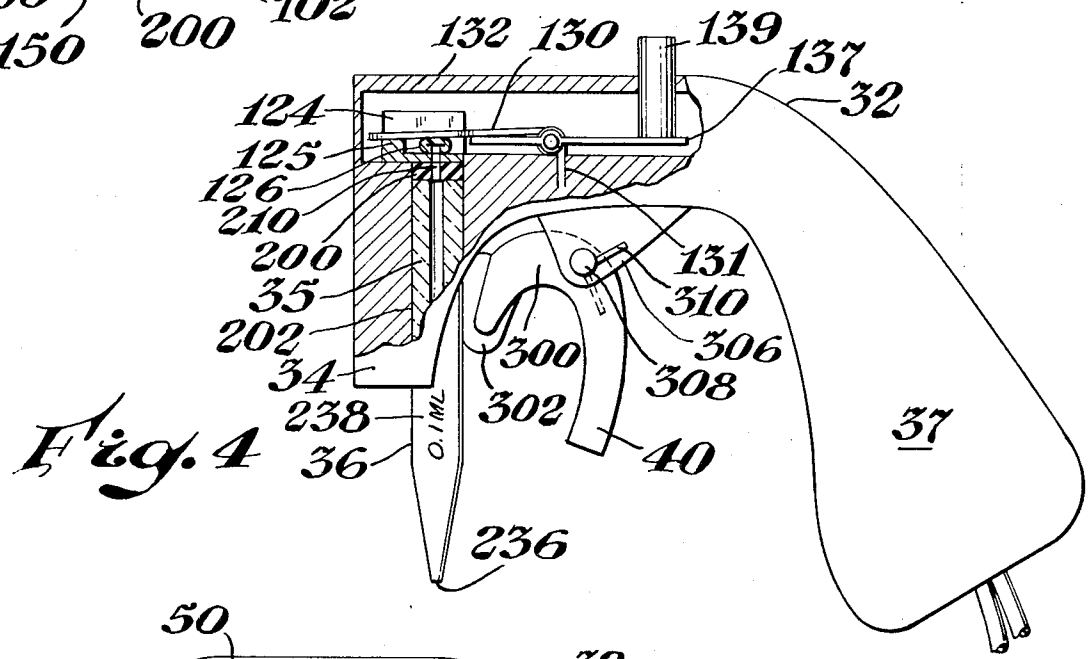

Fig. 4

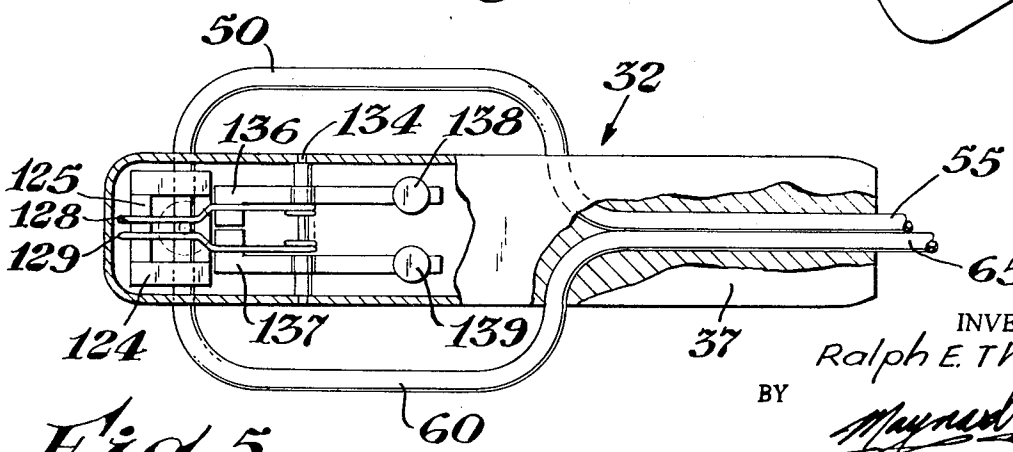

Fig. 5

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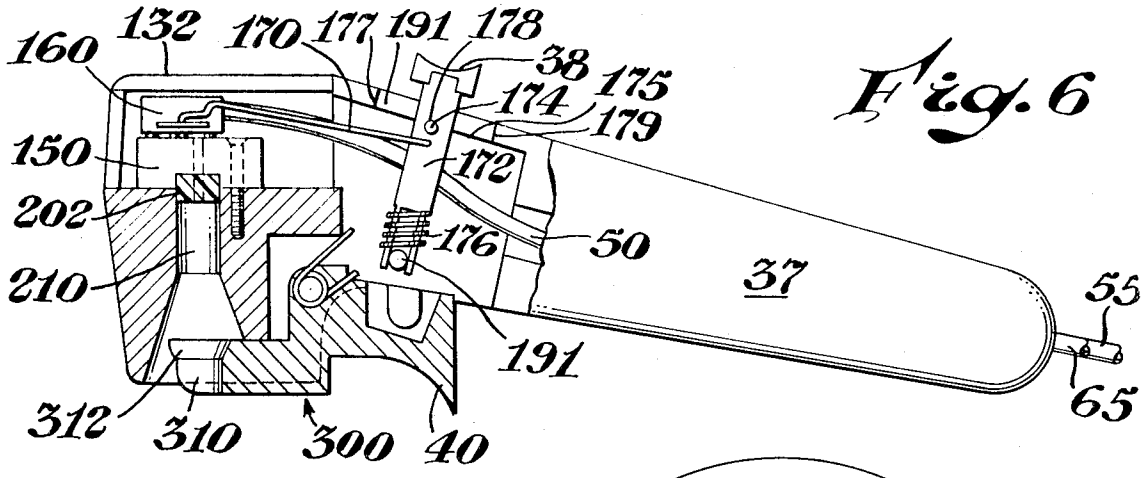

Fig. 6

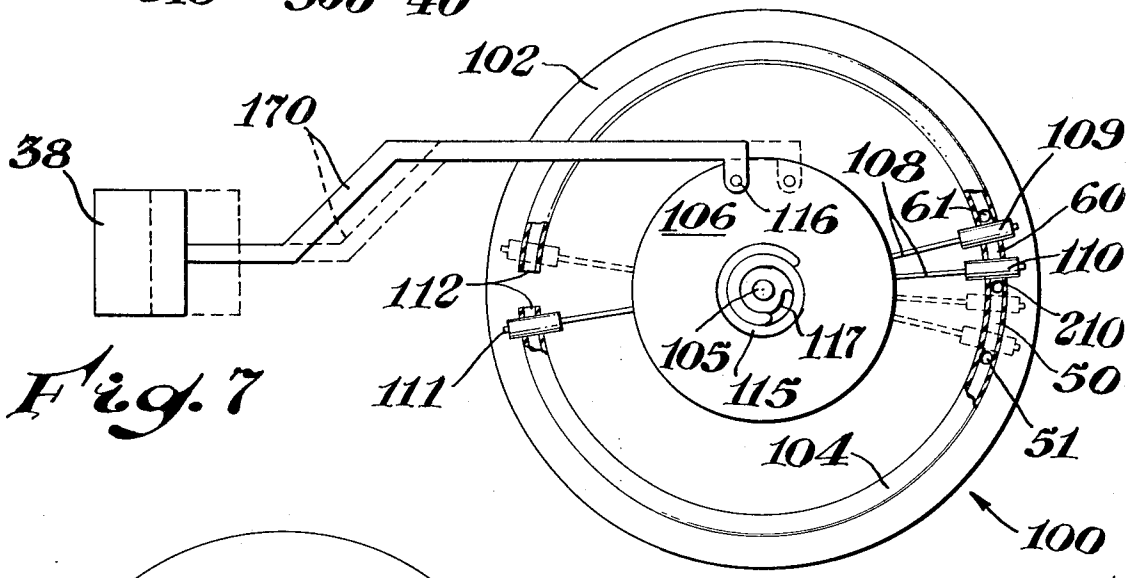

Fig. 7

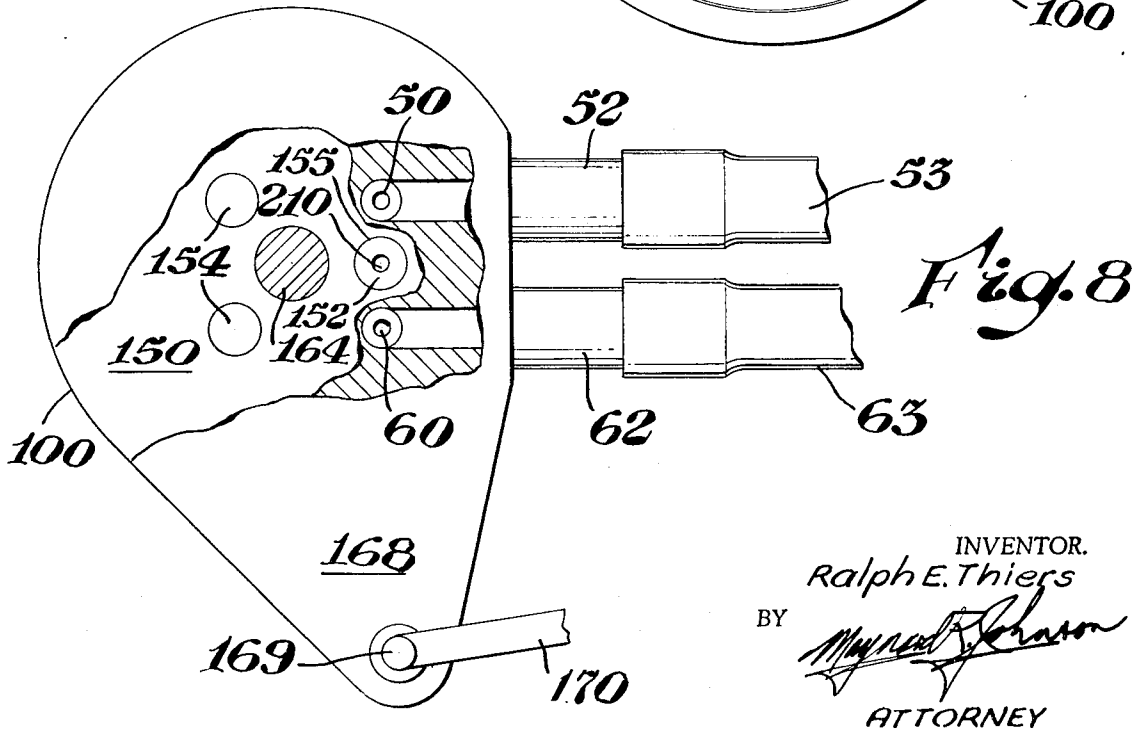

Fig. 8

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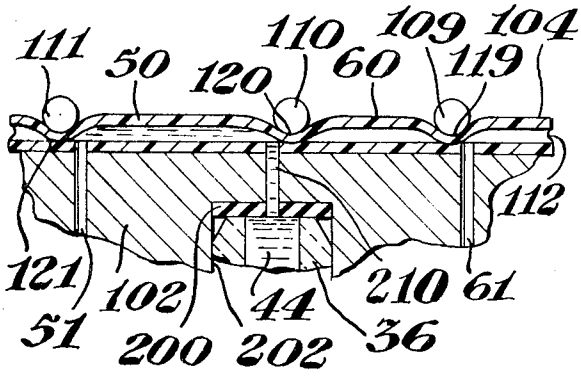

Fig. 10

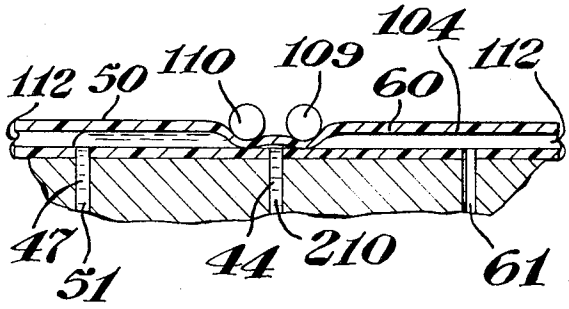

Fig. 11

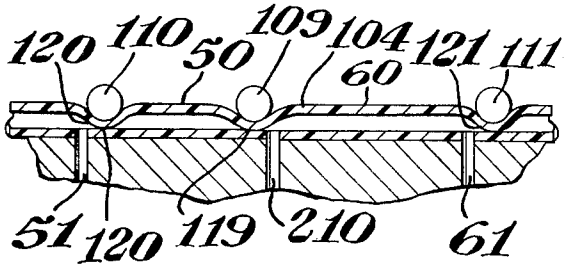

Fig. 12

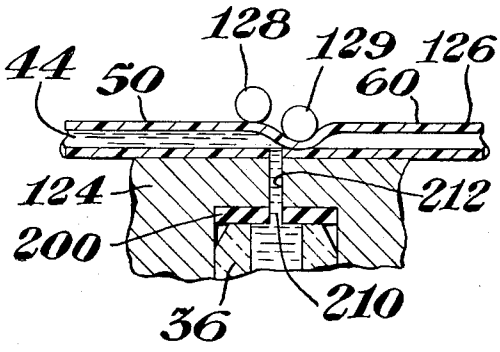

Fig. 13

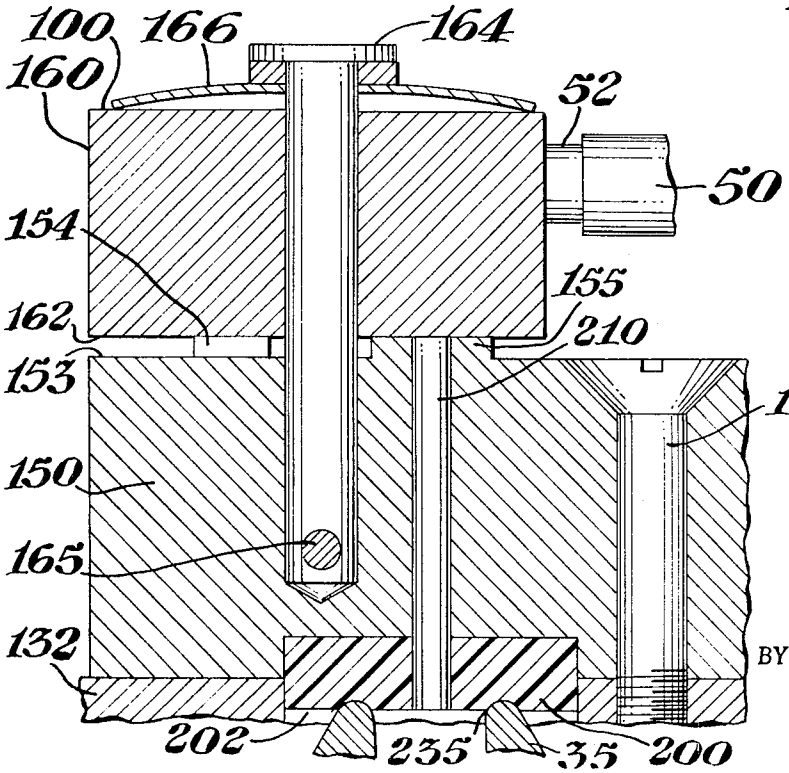

Fig. 9

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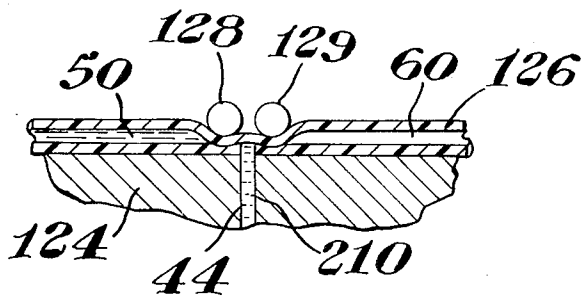

Fig. 14

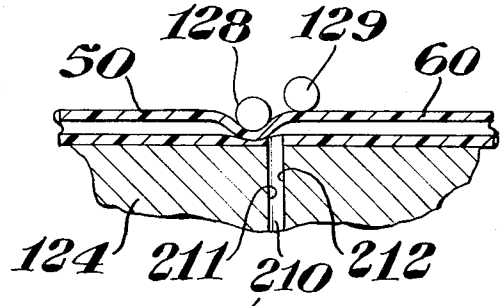

Fig. 15

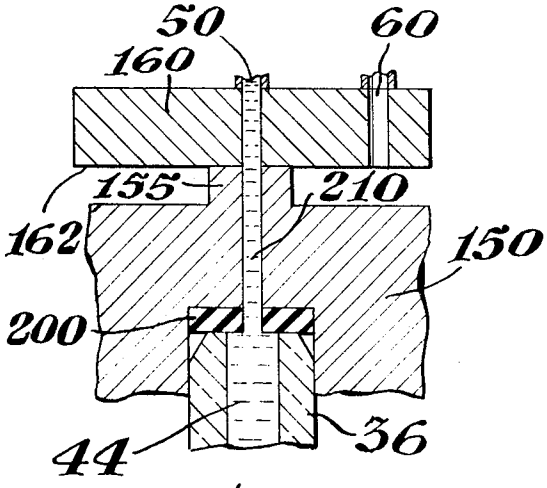

Fig. 16

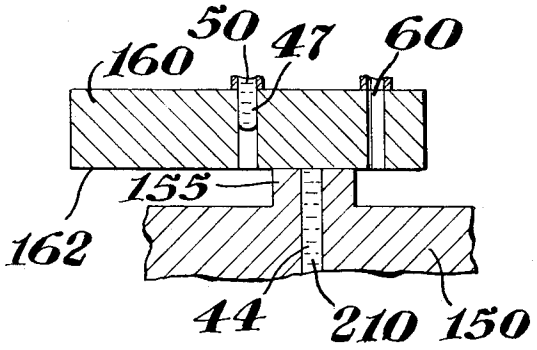

Fig. 17

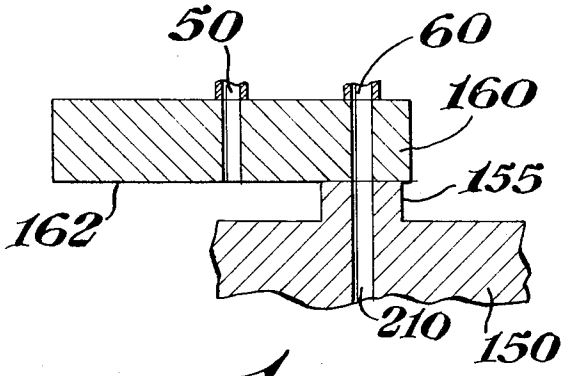

Fig. 18

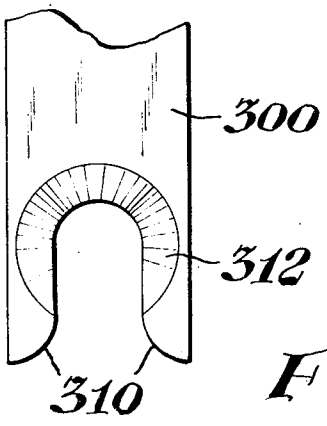

Fig. 19

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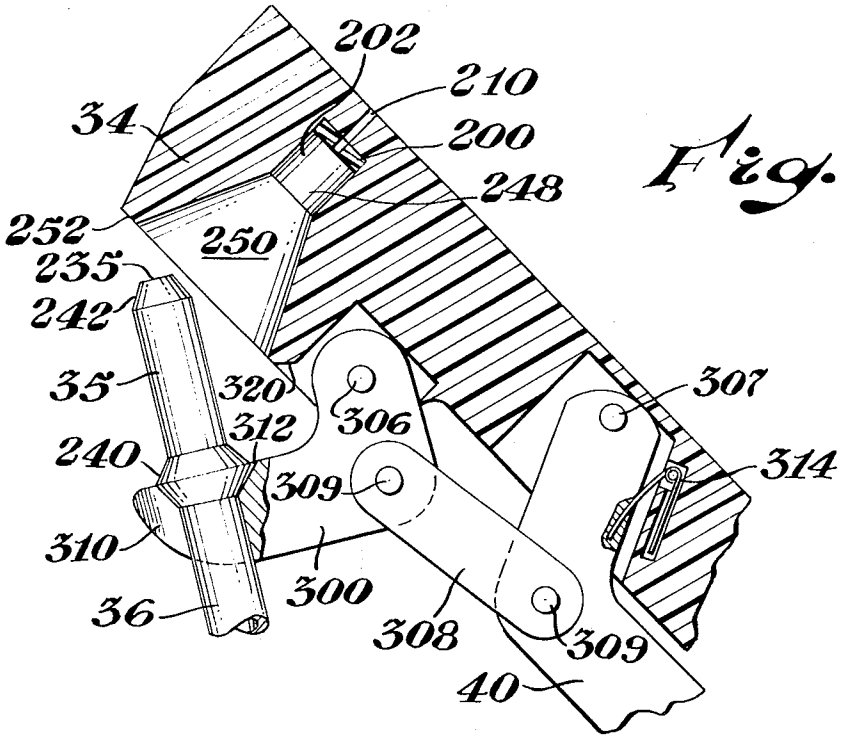

Fig. 20

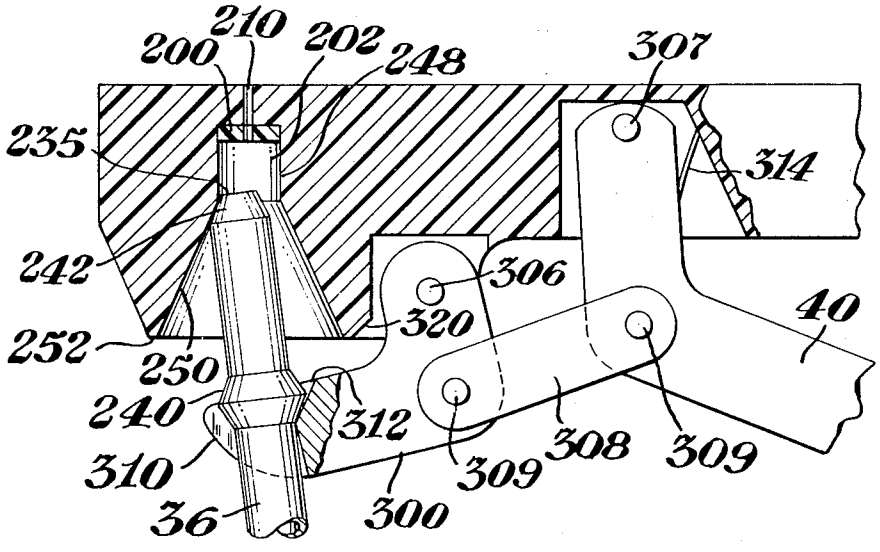

Fig. 21

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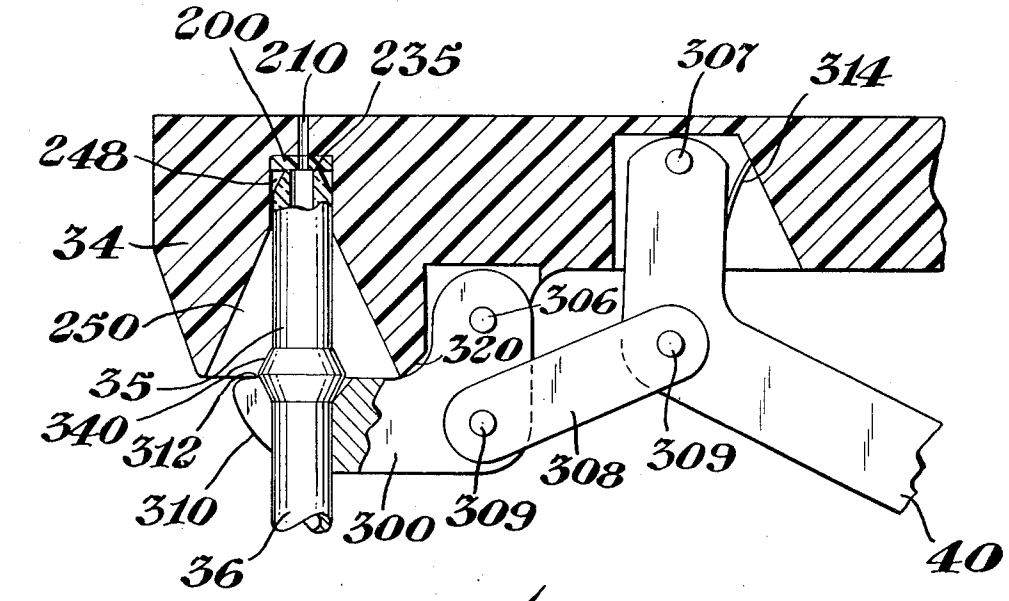

Fig. 22

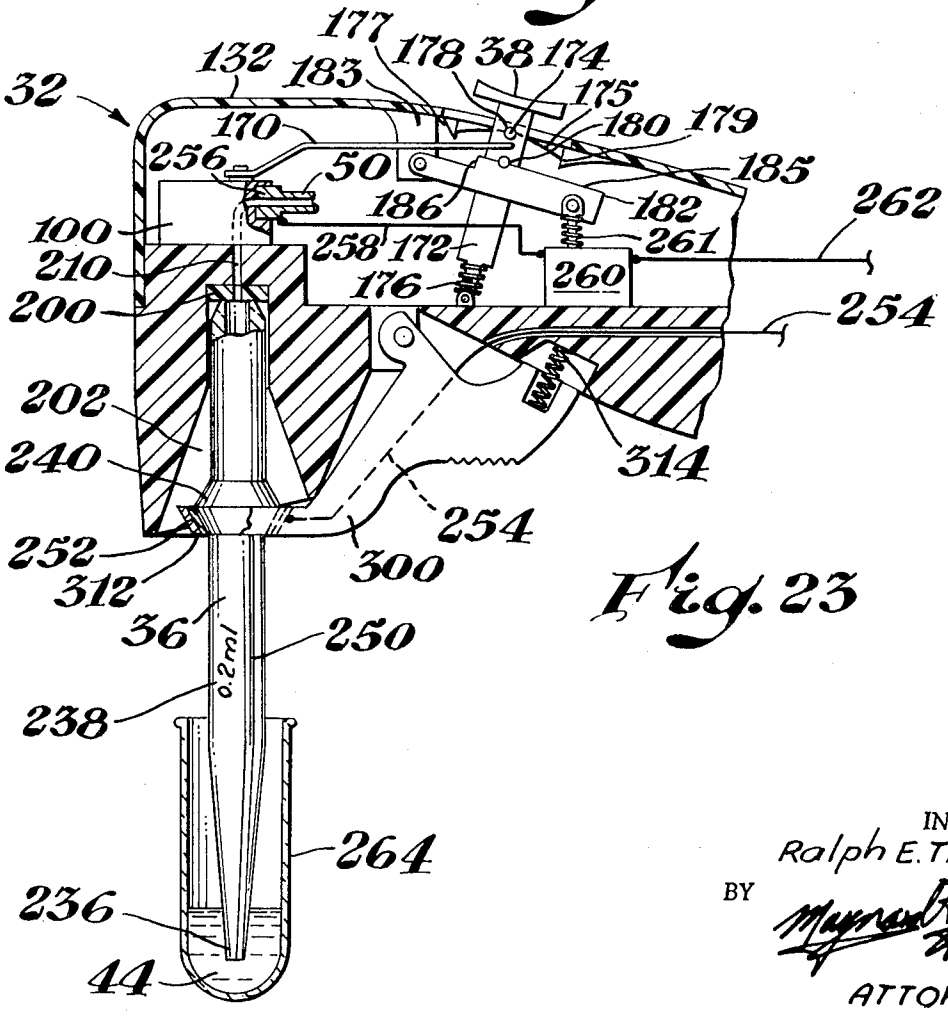

Fig. 23

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PIPETTING APPARATUS AND METHOD

CROSS REFERENCES TO RELATED APPLICATIONS

This is a continuation-in-part of my application Ser. No. 860,775, filed Sept. 24, 1969, now U.S. Pat. No. 3,607,082 which in turn is a continuation-in-part of my application Ser. No. 541,306, filed Apr. 8, 1966, now U.S. Pat. No. 3,475,128.

BACKGROUND OF THE INVENTION

The present invention is concerned with apparatus of the type generally referred to as "automatic pipets," including those devices which may also be described as semi-automatic. A wide variety of such apparatus is known, and automatic pipets have been classified into various groups of the same or similar types. Types of automatic pipets include both dispensers and dilutors; both mobile and immobile devices; both hand operated and mechanically operated devices; syringe-operated apparatus, such as the immobile dilutor of Rosen U. S. Pat. No. 3,197,285, and stopcock-type apparatus, such as the immobile device of Jungner, U. S. Pat. No. 3,476,518, and devices employing both a syringe and a stopcock, as illustrated by U. S. Pats. Nos. 3,138,290, 3,138,294, and 3,012,863; as well as various other devices such as tilt dispensers, double-action pipettes and rubber-bulb--operated pipets. See Broughton, A Guide to Automatic Pipettes, Technical Bulletin No. 6, Association of Clinical Biochemists, Scientific Committee, (1965).

Many of the devices are highly specialized, some individual devices can pipet only an invariant predetermined volume of liquid, while others require precise recalibration of syringes or the like in order to change the volume of liquid or liquids to be pipetted. Many of the devices are somewhat inflexible in that a single device cannot be employed for pipetting successive volumes of different liquids without extensive washing or cleaning of all the working surfaces each time a different liquid is to be pipetted.

Many of the automatic pipets in use are suitable for pipetting of aqueous fluids and liquids having a similar vapor pressure, but cannot be employed with low boiling liquids, such as diethyl ether, which have high vapor pressures under the conditions in which the pipet is used. The mobile devices can, in general, be moved from tube to tube as desired; however, many of the mobile devices depend on manual operation to a high degree. In contrast, the immobile devices cannot be moved during use, however, many of the immobile devices are highly automatic, providing "push button" simplicity of operation.

It would be desirable to provide a pipetting apparatus which is simple and accurate in operation, which is flexible in use both as to the types and volumetric amounts of liquids pipetted, and which can be mobile or immobile as desired while providing highly automatic, simple and foolproof operation.

BRIEF SUMMARY OF THE INVENTION

The pipetting apparatus of the invention comprises a pipet-operating subassembly operably engageable with pipet-driving means for providing pipet-charging suction and pipet-discharging pressure thereto and selectively operably engageable with a pipet, the pipet-operating subassembly including means for selectively operably engaging the pipet-driving means with a pipet selectively to charge the pipet by suction, to seal a predetermined volume of fluid within the pipet and to discharge the pipet under pressure. The pipet-operating subassembly can be mobile with respect to the pipet-driving means, which can be adapted to provide continuous suction and pressure to the pipet-operating subassembly by means of flexible tubes or other universally movable coupling means. The pipet-operating subassembly includes low dead space valve means for controlling the charging, sealing, and discharging of pipets. Also included on the pipet-operating subassembly are means for selectively operably engaging the pipet-operating subassembly with individual pipets to permit pipetting to be carried out with any desired individual pipet of a plurality of pipets of different volumes. The pipetting apparatus can also include a novel pipet or plurality of interchangeable pipets adapted to co-act with the pipet-operating subassembly. The apparatus of the invention is simple in construction and operation, highly flexible in use, and provides mobility in use coupled with highly automatic, precise pipetting of a wide variety of fluids. The invention also provides for rapid operation while minimizing errors. Other advantages of the invention will be apparent from consideration of the following description and claims and of the drawings.

BRIEF DESCRIPTION OF THE FIGURES OF THE DRAWINGS

FIG. 1 is an isometric view of a pipetting apparatus of the invention illustrating the use thereof in pipetting;

FIGS. 2 and 3 are schematic views of the apparatus of the invention in two embodiments thereof;

FIG. 4 is a side elevational view of a representative embodiment of a pipettor of the invention partially broken away to illustrate structure of the valving means, sealing means, valve operating means and pipet receiving and retaining means;

FIG. 5 is a plan view of the pipettor of FIG. 4, partially broken away to illustrate the valve and valve operating means;

FIG. 6 is an elevational view of a second embodiment of a pipettor of the invention, partially broken away to illustrate the valve operating means, valve means, sealing means, and pipet receiving and retaining means;

FIG. 7 is a plan view of the valving means of a pipettor of the invention in one embodiment thereof;

FIGS. 8 and 9 are plan and elevational views partly in section of a valve means in another embodiment thereof;

FIGS. 10, 11 and 12 illustrate the operation of the valving means embodiment of FIG. 7;

FIGS. 13, 14 and 15 illustrate the operation of the valving means embodiment of FIGS. 4 and 5;

FIGS. 16, 17 and 18 illustrate the operation of the valving means embodiment of FIGS. 8 and 9;

FIGS. 19, 20 and 21 and 22 illustrate the structure and operation of the pipet, pipet receiving means, sealing means and pipet retaining means of the invention in a representative embodiment thereof;

FIG. 23 is an elevational view of a pipet and pipettor of the invention partially broken away to illustrate a

further embodiment of the pipet and valve control means.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring more particularly to FIGS. 1–3 the pipetting apparatus **30** comprises a pipet-operating subassembly, e.g., pipettor **32**. Pipettor **32** includes a pipet-receiving portion **34** adapted to receive an end **35** of a pipet **36**, and a manually-graspable portion, e.g., handgrip **37** adapted to fit comfortably in the hand **25** of an operator. Means for operating the pipet **36**, such as hollow suction and pressure lines **50, 60** for supplying suction and pressure for charging and discharging pipet **36**, and the attendant valving means, e.g., valve **100**, for controlling application of suction or pressure to operate the pipet **36**; means for selectively sealing the end **35** of a pipet **36** in operative engagement with valve **100**, e.g., gasket **200**; pipet receiving means, e.g., socket **202** for guiding pipet **36** into operative engagement with gasket **200** and valving means **100**; and a pipet-retainer **300** are all housed in pipettor **32**, as are means for selectively operating the valve **100**, e.g., button **38**, and for selectively operating the pipet retainer, e.g., trigger grip **40**. The pipetting apparatus **30** further comprises a pipet-driving subassembly **80**. The pipet-operating subassembly **80** includes means for supplying pipet-operating suction and pressure to the pipettor **32**, e.g., suction and pressure pumps **82, 84** in FIG. **2**, or the intake and exhaust ports **86, 87** of a single pump **88** in FIG. **3** and the attendant hollow suction and pressure connecting lines **81, 83**, liquid trap **85**, trap connecting line **79**, motor or motors **89** and the like. The pipet-operating subassembly **80** is preferably mounted within a unitary housing **28**. Housing **28** preferably includes a receptacle **39** adapted to house the pipettor **32** when not in use, and a removable face plate **40** to provide access to the trap **85**, motor and pump means and the like enclosed within housing **38**. Control of the operation of the pump and motor means is conveniently provided by appropriate circuitry (conventional and not shown) operated by a switch button **41**, also mounted on the housing **28**. The pipettor **32** and pipet-driving subassembly **80** are operably engaged with each other by means of flexible suction and pressure tubes **55, 65** which communicate between the corresponding lines **50, 60** in the pipettor **32** and the corresponding pump means (pumps **82, 84** in FIG. **2** or intake and exhaust ports **86, 87** of pump **88** in FIG. **3**) by way of connecting lines **81, 83** in the housing **28**. Tubes **55, 65** are flexible to permit the pipettor **32** to be moved freely with respect to the housing **28**, as may be convenient in typical operation, for example, in pipetting a given quantity of a liquid **44** from a first beaker **45** to a second beaker **46**.

In operation, fluid suction (partial vacuum or reduced pressure) and fluid pressure for charging and discharging the pipet **36** are provided in the suction and pressure lines **50, 60** in pipettor **32** by means of the flexible tubes **55, 65** and pressures and suction means of subassembly **80**. Suction and pressure are thus supplied in a substantially continuous fashion at the valve **100** in pipettor **32**, fluctuations in fluid pressure within the system resulting primarily from the work done in charging and discharging a pipet **36** or from pressure regulating means as described below. The pipettor **32** is universally mobile in three dimensions with respect to subassembly **80**. Charging and discharging of the pipet **36** are carried out by means of valve **100** housed in the pipettor **32** whereby the pipettor-engaging end **35** of pipet **36** is selectively placed in communication with either the suction line **50** for charging or the pressure line **60** for discharging. The valving means employed also permits pipet end **35** to be sealed from communication with suction and pressures lines **50, 60** and sealed from the atmosphere as may be desired, for example, in transporting a charged pipet **36** from one beaker **45** to another beaker **46**. The apparatus **30** can be further characterized in that the pipetting operation involves complete charging of a pipet **36** with a liquid **44** to be measured, an initial portion of the liquid charged into pipet **36** being employed as a pre-wash liquid in each charging operation. The valve **100** employed in the pipettor **32** mechanically divides the metered portion of a charged liquid **44** from a pre-wash portion **47**, preferably by division at a single location. The pre-wash portion **47** remains in the pipettor **32**, and is carried along suction line **50** and tube **55** to trap **85** for ultimate disposal. The portion of fluid **44** metered in pipet **36** is mechanically and precisely separated from the pre-wash portion by the valve **100** and is ultimately discharged through pipet tip **236**. Complete charging of pipets **36** and mechanical division of the fluid **44** eliminates many of the problems encountered in pipetting of volatile liquids.

The volume of fluid pipetted is the total of internal volume of the pipet **36** plus the volume of a micropipet **210** which communicates with pipet **36** independently of whether valve **100** is in the sealing, charging or discharging mode of its operation. Micropipet **210**, as illustrated in FIGS. **11, 14** and **17**, for example, is defined by those portions of valve **100** and gasket **200** which enclose a portion of fluid **44** which is to be discharged through pipet **36**. The metering operation thus does not depend upon charging to a meniscus line as in manual pipetting, or upon calibration of the displacement of a piston, as in syringe metering. The volume of the micropipet **210** of a pipettor **32** is small in relation to he volume of the pipet **36** itself. For example, the micropipet volume can be on the order of from about **1** microliter or less to about **10** to **15** microliters, or on the order of one percent or less to **10** to **15** percent or more of the total volume pipetted, depending on the volume of the particular pipet **36** employed. The volume of fluid **44** metered by the micropipet **210** is substantially uniform from one pipetting operation to another, regardless of whether the same or different pipets **36** having the same or different volumes are employed. Consequently, pipetting of different volumes is readily carried out by employing a plurality of pipets **36**, each calibrated to contain and deliver a desired volume of fluid in conjunction with the micropipet **210**. As will be more fully described hereinbelow, the coaction of the various pipet-operating and pipet engaging and retaining means elements of the pipettor **32** with pipets **36** of various sizes and with the other elements of the apparatus **30** provides a versatile integrated pipetting apparatus capable of rapid and accurate pipetting of fluids over a wide range of volumes.

Further advantages of the invention and additional details of the construction and operation thereof will be apparent from consideration of the following detailed description of preferred embodiments of the invention. In the following description it will be convenient to refer separately to various elements of the pipetting apparatus **30** and embodiments of such elements. For ease of reference, the same reference characters are employed from time to time in the drawings to refer to identical elements as they appear in different embodiments of the invention.

1. THE PIPET-DRIVING SUBASSEMBLY 80, CONNECTING TUBES 55, 65 AND SUCTION AND PRESSURE LINES 50, 60

The supply of pipet-driving suction and pressure at valve **100** in pipettor **32** is substantially continuous regardless of whether valve **100** is in a charging, sealing or discharging mode of operation. Consequently, it will be convenient to describe the means of supplying and regulating suction and pressure separately from a detailed description of preferred embodiments of valve **100**.

Referring more particularly to FIGS. 1–3, pipet-charging suction and discharging pressure are furnished by suction and pressure pumps **82, 84** or by a single pump **88**. Conventional air pumps capable of providing, for example, a partial vacuum and positive air pressure on the order of about 1 to 5 pounds per square inch gauge can be employed, the pumps **82, 84, 88** being driven by an electric motor or motors **89** or other suitable means. When desired, a pressurized gas cylinder, aspirator or other means for providing fluid pressure and suction can be employed, and discharge pressure can also be provided in the form of a liquid inert to the material to be pipetted, although gas pressure is generally suitable and convenient. Trap **85** can be a conventional liquid trap for preventing liquid from reaching pump **82** or **88**, while maintaining a partial vacuum in line **50** and tube **55**. The tubes **79, 81, 83, 55, 65** and suction and pressure lines **50, 60** are conveniently flexible, hollow tubing of a polymeric material such as polyethylene, rubber, plasticized polyvinyl chloride, polypropylene, or the like, and are preferably resilient and transparent. Flexible tubing having an inside diameter of from about 1 to about 10 millimeters and an outside diameter of from about 4 to about 20 millimeters, can be conveniently employed. It is preferred, however, that suction connecting tube **55** be of a material which is easily wetted by the liquid or liquids to be pipetted, a connecting tube **55** of rubber being preferred, for example, for pipetting aqueous liquids. In typical repetitive pipetting operation, suction connecting line **55** can contain several successive portions of pre-wash liquid **47** as the liquid portions are drawn under suction to trap **85**. The use of a connecting tube **55** of wettable material substantially reduces the suction required to draw several portions of pre-wash liquid **47** from pipettor **32** to the trap **85** as well as contributing to uniformity of suction applied at valve **100** during a series of rapid successive pipetting operations. Connecting tubes **55, 65** are coupled to the corresponding connecting lines **79, 83** at the pipet-driving subassembly housing **28** and to lines **50, 60** or portions thereof in the pipettor **32** by friction fit over tubular couplings **90** or by any other suitable coupling means.

The fluid circuit connecting the valve **100** and pumps **82** and **84** or **88** can include means for regulating the pressure and suction applied at the valve **100**. For example, low pressure differentials at the valving structure **100** can be desirable to provide low flow rates when small volumes (e.g., 100 microliters to a few milliliters) are being pipetted, and high pressure differentials may be desirable for more rapid charging and discharging of large volumes (e.g., 25 or 50 milliliters). Pressure and suction can be regulated independently by an adjustable screw clamp **91** on each of connecting lines **55, 65** as shown in FIG. 2. Clamps **91** may be mounted in the pipettor **32**, within the housing **28**, or on external portions of tubes **55** and **65** themselves. Alternately, pressure and suction pressure differentials can be regulated by a surge chamber **92** in the pressure connecting line **83**, chamber **92** being vented to the atmosphere via an adjustable pressure relief valve **93**. As illustrated in FIG. 3, adjustment of the pressure relief valve **93** provides direct control of the maximum pressure in lines **83** and **60**, tube **65** and surge chamber **92**. Valve **93** indirectly controls the suction by controlling the exhaust pressure of pump **88**. Direct control of suction line pressure can be obtained by employing a similar surge chamber and pressure relief valve in the suction connecting line **81** downstream of trap **85**. In convenient form the vented surge chamber **92** can comprise a short length of flexible tubing intersecting line **83** or line **81** at a T or Y intersection, with a screw clamp or other adjustable clamp for sealing the tubing against selected pressure differentials serving as valve **93**. In charging a pipet **36**, a pre-wash portion of liquid **47** is carried through valve **100** into suction line **50**. Line **50** and the pipettor **32** preferably include a transparent portion, view port or the like to permit visual observation of line **50**, so that the movement of a liquid column into line **50** provides a visible indication to an operator that charging is complete. A fixed fluid resistance **95**, such as a constriction in the suction line provided by a tubular coupling **90** in FIG. 2, is provided to impede the flow of the liquid column along the suction line **50** toward trap **85** and to reduce the volumetric liquid flow rate in line **50**, after the charged liquid reaches the constriction or resistance **95**. The reduction in flow rate facilitates observation of completion of charging and reduces the volume of liquid which may be inadvertently drawn into suction line **50** when sealing of the charged micropipet **210** is delayed by operator inattentiveness or the like. A similar fluid resistance or constriction **95** can be disposed in pressure line **60** to limit the volume of pressurized discharge gas which enters the valving structure at the initiation of discharging, thus providing for a steady, even flow of pressurized gas regardless of the initial pressure differential between pressure line **60** and micropipet **210** when discharging is begun. The fluid resistance or constriction **95** is preferably disposed in pressure line **60** so that the internal volume of line **60** downstream of the resistance **95** with respect to fluid flow therethrough is less than the smallest volume of fluid to be pipetted with the pipettor **32**. The discharge gas volume contained in line **60** downstream of resistance **95** is preferably sufficiently small in relation to the pipet volume to provide a substantially uniform flow rate from the pipet **36** during a major proportion of the discharging operation regardless of pressure increases

in the suction line **60** when the valve structure **100** is sealed.

2. THE VALVE 100

a. A First Preferred Embodiment

In one embodiment thereof, the valve **100** employs principles of structure and operation described in my application Ser. No. 541,306, filed Apr. 8, 1966, now U. S. Pat. 3,475,128.

As illustrated in FIGS. **7** and **10–12**, the valve **100** can comprise a relatively rigid base **102** which can be part of the pipet-receiving portion **34** of a pipettor **32**, the base **102** having a partially circular movable, tubular conduit wall **104** secured thereto, portions of conduit wall **104** defining portions of suction and pressure lines **50, 60**. Valve **100** also comprises a spider **106** pivotally mounted on base **102** by means of a shaft **105**. Spider **106** carries rollers **109, 110, 111** rotatably mounted on the arms **108** of the spider **106**, the rollers **109, 110, 111** being disposed against portions of the conduit wall **104** so as to compress opposed portions of conduit wall **104** together between each roller **109, 110, 111** and the base **102** thus forming a series of movable seals **119, 120, 121** in lines **50, 60**. Conduit wall **104** is preferably of a resilient material adapted to maintain lines **50, 60** normally open. Base **102** also includes a pipet-receiving socket **202** having a gasket **200** mounted therein and adapted to sealingly engage a pipet **36**. Fluid communication between lines **50, 60** and the pipet **36** is provided by a micropipet bore **210** extending through conduit wall **104**, through base **102** and gasket **200**. The bore **210** thus constitutes a micropipet chamber which is continuously in communication with socket **202** or the interior of a pipet **36** and which is selectively in communication with portions of lines **50, 60** within conduit wall **104** at a generally T-shaped intersection. Pressure line **60** and suction line **50** similarly communicate with other portions of lines **50, 60** externally of valve **100** via pressure and suction line bores **61, 51** through conduit wall **104** on either side of, and adjacent to the intersection of lines **50** and **60** and micropipet bore **210**. Beyond suction and pressure line bores **51, 61** and more or less diametrically opposed to micropipet bore **210** on base **102**, the conduit wall **104** terminates in vents **112**, adapted to provide communication between lines **50** and **60** and the atmosphere. The volume enclosed by conduit wall **104** between vent **112** and micropipet **210** and including suction line bore **51** thus corresponds to that portion of a suction line **50** included in valve **100**. A corresponding volume enclosed by conduit wall **104** and pressure line bore **61** constitutes a corresponding portion of a pressure line **60**. The valve **100** is housed in a pipettor (not shown in FIG. **7**) and coupled via continuations of lines **50, 60** and appropriate tubes to a driving subassembly.

Spider **106** is pivotally connected by a pin **116** to a push rod **170**, the rod **170** being in turn connected to an actuator button **38** or control lever (not shown in FIG. **7**). Linear motion of actuator button **38** and rod **115** rotates spider **106** with respect to base **102** and conduit **104**, moving the rollers **109, 110, 111** and seals **119, 120, 121** along conduit wall **104** thereby sealing selected portions of lines **50, 60** and placing valve **100** in one or another of the pipet-charging, metering, and discharging modes, illustrated in FIGS. **10-12**. A torsion spring **115** secured to spider **106** and through slot **117** in spider **106**, also secured to base **102**, provides means for biasing the valve **100** toward the pipet-sealing mode schematically illustrated in FIG. **11**.

In the charging mode the rollers **109, 110, 111** and seals **119, 120, 121** are disposed as shown in the solid lines of FIG. **7** and schematically illustrated in FIG. **10**, with rollers **109, 110** moving opposed portions of conduit wall **104** together to form seals **119, 120** in the pressure line **60** between the micropipet **210** and pressure line bore **61** while leaving pressure line **60** open between pressure line bore **61** and its vent **112**. Roller **111** forms a seal **121** in suction line **50** between bore **151** and vent **112**. The suction line **50** is in communication with the pipet **36** through micropipet **210** and sealed from the vent **112**, permitting a fluid **44** to be drawn into pipet **36**, micropipet **210** and through line **50** and bore **51**.

Movement of the spider **106** in a clockwise direction with respect to FIG. **7** moves the rollers **109, 110** and the seals **119, 120** formed thereby to the position illustrated schematically by FIG. **11** with portions of conduit wall **104** compressed together normally across both lines **50, 60** so that seals **119, 120** are formed in the conduit wall portions surrounding micropipet **210**. In such position seals **109, 110** seal the fluid to be metered **44** within micropipet bore **210** and pipet **36**. The movement of seal **120** across bore **210** mechanically divides the fluid **44** and seals a pre-wash portion thereof **47** in the suction line **50** to be drawn off by suction. Both the suction and pressure lines **50, 60** are open to their vents **112** in this position, the conduit wall portions **104** at vents **112** being spaced sufficiently apart so that both vents **112** remain open when roller **111** is positioned therebetween.

Further clockwise motion of the spider **106** to the position illustrated by the broken lines of FIG. **7** results in movement of roller **109** along conduit wall **104** toward the suction line **50**, moving seal **119** across micropipet **210** to the position in line **50** shown schematically in FIG. **12**. Roller **110** and seal **120** are moved progressively along the suction line **50** to suction line bore **51**, thus carrying any portion of pre-wash fluid **47** to suction line bore **51**, and ensuring the removal thereof from the valve **100** prior to the next cycle of operation. Roller **111** and seal **121** are simultaneously moved to seal the pressure line **70** from its vent **112**, so that discharge fluid pressure from bore **61**, e.g. air from pressure pump **84** or the exhaust port **87** of pump **88**, is directed through line **60** into micropipet **210** and pipet **36** to discharge the metered fluid **44**. After discharging, the valve **100** is returned to the mode shown in solid lines in FIG. **7** and illustrated in FIG. **10** to repeat the cycle, or to the intermediate position of FIG. **11**, with micropipet **210** sealed and lines **50, 60** open to vents **112**, for changing pipets or otherwise manipulating the pipettor prior to charging. This embodiment of valve **100** provides venting of suction and pressure lines **50, 60** to atmosphere when said lines are not in communication with micropipet **210**, thereby minimizing excessive loads on the pump or pumps **82, 84, 88** and wide variations in pressure or partial vacuum in lines **50, 60**. Since lines **50, 60** are open either to a vent **112** or to micropipet **210** at all times, a single pump **88** can be employed.

b. A Second Preferred Embodiment

As illustrated in FIGS. 4, 5 and 13–15, in a second embodiment, a second valve embodiment **100** comprises a rigid base **124**, which can be fabricated of rigid plastic, glass, metal or the like and which can be of unitary construction with the receiving portion **34** of a pipettor **32**. Mounted on base **124** are pressure lines **50** and **60**, said lines having a unitary movable tubular wall **126**, similar to the conduit wall **104** of the embodiment described above. A micropipet **210** extends through base **124** and a tube wall **126**, forming one arm of a three-way intersection with suction and pressure lines **50, 60**. A double torsion spring **130** is mounted on pin **134** within pipettor **32**, having a tail portion **131** thereof securely mounted within the pipettor body **132**. First and second movable arms **128, 129** of spring **130** are disposed across lines **50, 60** to maintain the lines normally closed by compressing opposed portions of tube wall **126** together against base **124** as shown in FIG. **14**. First and second levers **136, 137** are pivotally mounted within pipettor **32** on pin **134**, a portion of each lever **136, 137** extending under one of the respective arms **128, 129** of spring **30**. Charge and discharge control buttons **138, 139** are slidably mounted in the pipettor **32**, extending internally thereof through the pipettor body **132** to operably engage first and second levers **136, 137**, respectively. Upon manual depression of the charge control button **138** lever **136** moves pivotally on pin **134** as a fulcrum, lifting spring arm **128** from the tube wall **126** of line **50**, thereby opening suction line **50** for charging as illustrated in FIG. **13**. Similarly, depression of button **139** moves lever **137** pivotally on pin **134**, lifting spring arm **129** from tube wall **126** and base **124** and opening pressure line **60** for discharging as illustrated in FIG. **15**. In the absence of manual depression of buttons **138, 139**, both spring arms **128, 129** are biased against portions of tube wall **126** to compress the same against the opposed wall portions surrounding micropipet **210** thus sealing lines **50, 60** from the micropipet bore **210** as shown in FIG. **14**. The bias provided by spring **130** also serves to lift both control buttons **138, 139** through the action of the spring arms **128, 129** on levers **136, 137** returning them to a normal, undepressed position.

The valve base **124** preferably includes a rigid spring arm stop **125** extending upwardly therefrom toward spring arms **128, 129** a distance greater than the thickness of a wall of tube **126** and preferably slightly less than twice such wall thickness. When the arms **128, 129** are in line sealing engagement with tube wall **126**, stop **125** limits their motion toward base **124**. The thickness of stop **125** is selected so that a spring arm **128, 129** can be biased against tube wall **126** with a force far in excess of that required to seal lines **50, 60** without unduly deforming or damaging the tube wall **126**. Stop **125** permits compression of tube wall **126** by the spring arms **128, 129** to a distance less than two wall diameters to enhance sealing and bring about deformation of the tube wall **126** sufficient to seal any internal surface imperfections, while preventing undesired volumetric distortion of lines **50, 60** at the intersection with the micropipet bore **210**. By employing a stop **125**, lines **50** and **60** can be sealed while employing line pressures much greater than would otherwise be possible without damage to the tube wall **126**.

The micropipet **210** is cylindrical, and the spring arms **128, 129** are preferably disposed for movement in parallel planes tangential to diametrically opposed walls **211, 212** of the micropipet **210**. Such arrangement facilitates precision sealing since the portion of the tube wall **126** moved by a spring arm **128, 129** then is compressed against an opposed wall portion which is tangential to micropipet **210**, that is, at the intersection of the tube wall **126** with one of the opposed walls **211, 212** of the micropipet **210**. Sealing of one or another of lines **50, 60** in this manner serves to convert the three-way intersection of lines **50, 60** and bore **210** to a two-way intersection of bore **210** with a single one of the lines. When the volume defined by the tube wall **126**, e.g., lines **50, 60**, has the same diameter as micropipet bore **210**, the two-way intersection thus formed has a substantially circular cross-section of substantially the same diameter as the micropipet bore **210** and open line (**50** or **60** as the case may be) and has a substantially smooth wall. Such structure within the valve **100** reduces or eliminates eddy currents during charging and reduces the volume of pre-wash fluid necessary to prevent carry-over of liquid from one pipetting operation to the next.

As shown in FIGS. **4** and **5**, lines **50, 60** extend beyond the valve structure **100** and pipettor **32**, being enclosed within the pipettor handgrip **37** and ultimately coupled to the suction and pressure connecting tubes **55, 65**. The pipet-receiving portion **34** of the pipettor **32** includes a gasket **200** of rubber, silicone rubber or the like seated against the base **124** of valve structure and a pipet-receiving socket **202** adapted to enclose an end **35** of a pipet **36**. A pipet **36** enclosed within the socket **202** and seated against gasket **200**, is selectively retained in position by a trigger-grip type of retainer **300**. Retainer **300** includes a pipet-gripping contact **302** of rubber or the like adapted to functionally engage the pipet, and a trigger grip **40**. The retainer **300** is mounted on pipettor **32** for pivotal movement with respect thereto, conventional mounting means, e.g. a flange **306** and pin **308**, being employed. A torsion spring **310** mounted on pin **308** maintains retainer **300** normally biased toward a pipet-retaining position illustrated in FIG. **4** with contact **302** biased toward socket **202**. A pipet **36** is gripped between the contact **302** and the opposed wall of the socket **202**, e.g., the pipet-receiving portion **34** of pipettor **32**.

With a pipet **36** thus engaged, and the suction and pressure lines **50, 60** connected to the appropriate suction and pressure pumps **82, 84** this embodiment of valve **100** is operated as illustrated in FIGS. **13-15**. Manual depression of control button **138** disengages spring arm **128** from tube **126**, opening line **50**. As shown in FIG. **13**, a column of fluid to be pipetted **44** is drawn into pipet **36**, micropipet **210** and suction line **50**. Release of charge control button **138** allows arm **128** to compress tube **126**, sealing line **50** and dividing pre-wash fluid portion **47** in suction line **50** from the metered fluid **44** in the pipet **36** and micropipet **210** (FIG. **14**). The pre-wash fluid portion **47** is continuously subjected to suction in line **50** regardless of further operation of the valve **100** and is ultimately drawn off along suction line **50** and connecting line **55**. In discharging, control button **139** is depressed so that lever arm **137** pivots and disengages spring arm **129**

from tube 126 to open pressure line 60. Suction line 50 remains sealed tangentially of micropipet bore 210 as shown in FIG. 15 while gas pressure provided through line 60 discharges the metered fluid 44 from the micropipet 210 and pipet 36.

c. A Third Preferred Embodiment

In the embodiment illustrated in FIGS. 6, 8, 9 and 16–18, the valve 100 comprises a base 150 mounted in the pipettor body 132 by conventional mounting means, e.g., mounting screw 151. A gasket 200 is mounted against base 150 and within socket 202. A cylindrical bore, micropipet 210, extends through gasket 200 and base 150. A pair of cylindrical studs 154 extend from base 150 a short distance, for example, 0.1 to 2 millimeters, beyond the upper face 153 of base 150. A hollow stud 155 also extends beyond the upper face 153 of base 150 and surrounds micropipet 210. Hollow stud 155 terminates in a sealing face 152, the face 152 preferably being a planar sealable surface in a plane normal to the axis of micropipet 210 and extending radially outward from micropipet 210 a distance preferably between one and two times the diameter of micropipet 210.

Valve 100 also comprises a block 160 which defines the portion of suction and pressure lines 50, 60 within the valve 100, block 160 being rotatably mounted on base 150 by a pivot pin 164 which is secured to base by conventional means, e.g., locking pin 165. Means for rotating block 160 are mounted thereon, including a radial arm 168 extending outwardly from block 160 and pivot pin 164, and connecting rod 170 pivotally coupled to arm 168 by a pin 169. Rod 170 is coupled at another portion thereof to control lever 172 and control button 38, so that reciprocating linear motion of button 38 and lever 172 is translated via rod 170, pin 169 and arm 168 to produce reciprocating rotary movement of block 160 about pivot pin 164.

Block 160 includes a face 162 slidably engaged against the studs 154 and sealing face 152 of hollow stud 155 so that face 162 can be slidingly and sealingly engaged with the face 162 of hollow stud 155 at all times. Block 160 is biased toward slidingly sealable engagement with hollow stud 155 by a conventional biasing means, e.g., spring washer 166 mounted on pin 164, the biasing pressure being distributed among studs 154 and stud 155. A flexible-walled suction line portion 53 and a flexible-walled pressure line portion 63 are coupled to block 160 by hollow tubular couplings 52, 62 to communicate with the respective corresponding lines 50 and 60 which extend through the block 160 and face 162. The pressure and suction lines 60, 50 as defined by the block 160 are of the same cross-sectional configuration and area as micropipet bore 210. It is preferred that the portions of lines 50, 60 in the region of the block face 162 be cylindrical bores in block 160 through face 162 having their axes parallel to the axis of micropipet 210 so that alignment of either of lines 50, 60 with micropipet bore 210 as illustrated in FIGS. 16 and 18 defines a continuous, smooth walled tubular bore extending through the valve 100 from the gasket 200 through base 150, stud 155 and into block 160.

The base 150 and block 160 can be fabricated from rigid materials which are inert to the fluids to be pipetted. For example, glass, high density polyethylene, acrylic resins, polytetrafluoroethylene, stainless steel and the like can be employed. The base 150 must be of material which is sufficiently rigid to prevent significant detectable deformation or volumetric distortion in the micropipet 210 under conditions of use and must also be resistant and inert to the fluids to be pipetted. The face 162 of block 160 also contacts the pipetted fluid and serves to seal and define the volume of fluid metered in the micropipet 210, and should likewise be resistant and inert to the fluid as well as being dimensionally stable in use. Glass or stainless steel and polytetrafluoroethylene polymers are preferred materials for fabrication of block 160. Additionally, it has been found that improved precision and ease of operation can be achieved when the materials of the block 160, at least at face 162, and at least the hollow stud extension 155 of the base 150 are of different compressive strength. The differential compressive strength should be such as to provide a tight seal by compression of the sealing face stud 155 against block face 162 under the bias of spring washer 166 despite minor surface irregularities, and to provide a wiping effect during sliding motion of the block 160 relative to base 150. Additionally it is preferred to fabricate the base 150 from material which is not wetted by the fluid materials to be handled. For general use, a base 150 of a polytetrafluoroethylene polymer, and a block 160 of stainless steel, glass or composite polytetrafluoroethylene material provide the desired hardness differential and wettability characteristics.

FIGS. 16, 17 and 18 illustrate the charging, sealing and discharging phases of a typical pipetting operation carried out with this embodiment of the valve 100. With a pipet 36 in position against gasket 200, and with the suction and pressure lines 50, 60 coupled via the appropriate couplings and connecting lines to suction and pressure pumps 82, 84 or to the intake and exhaust ports 86, 87 of a single pump 88, suction is continually applied in suction line 50 and pressure is continually supplied in line 60.

For charging, button 38 and lever 172 are manually moved toward the valve 100, rotating block 160 about pivot pin 164 and aligning suction line 50 with micropipet 210 as illustrated in FIG. 16. Pressure line 60, being spaced in block 160 a distance greater than the wall-thickness of hollow stud 155, is vented to atmosphere. When charging is completed, that is, when a column of fluid 44 has been drawn through pipet 36 and micropipet 210 into suction line 50, the control button and lever 38, 172 are moved to rotate block 160 to the position illustrated in FIG. 17. In such rotation, block 160 seals micropipet 210, retaining the metered volume of fluid 44. In the sliding motion of block 160 relative to base 150, stud 155 and micropipet 210, the valve 100 first divides a pre-wash fluid portion 47 from the metered fluid 44 as a portion of face 162 of block 160 surrounding suction line 50 slides across the face of stud 155 while simultaneously sealing the micropipet 210 with another portion of the block face 162. Further sliding motion of block 160 vents the suction line 50 to atmosphere as the pre-wash fluid 47 is drawn off along line 50, also providing air washing of line 50 during the sealing and discharging phases.

When discharging is desired, control button 38 and lever 172 are manually displaced away from the valve structure 100, rotating block 160 in a counter-

clockwise direction with respect to FIG. 8. Pressure line 60 is thereby aligned with micropipet 210 for discharging, while suction line 50 remains vented to atmosphere as illustrated in FIG. 18.

In each of the above-described three embodiments, the valve 100 provides selective communication of the micropipet 210 with one or another of the suction line 50 or pressure line 60 or selective sealing of the micropipet 210. The selective communication and sealing is carried out by moving selected wall portions of the suction or pressure lines 50, 60 to seal the lines, preferably by moving the wall portions in a plane normal to the axis of the line or lines. In the first embodiment the lines 50, 60 are sealed by compression of portions of their movable common wall, conduit wall 104 to form a series of movable seals 119, 120, 121 and moving the seals 119, 120, 121 along the suction and pressure lines 50, 60. In the second embodiment, lines 50, 60 are sealed by compressing selected movable opposed portions of the tube wall 126 together. In the third above-described embodiment, the block 160 constitutes a movable wall of both the suction and pressure lines 50, 60, the selective sealing of lines 50, 60 being carried out by moving the wall portions of said lines, i.e., block 160 with respect to wall portions of the micropipet 210, i.e., hollow stud 155 and base 150.

It will also be apparent from the above description that the valve 100 employed in the pipetting apparatus 30 permits the surface area of the selectively established seals to be minimized. For example, in a valve 100 according to the embodiment of FIGS. 16–18 the lines 50, 60 and micropipet 210 can have a diameter of about one millimeter, with cylindrical stud 155 having an outside diameter of slightly over 3 millimeters, the resulting surface area of slidable sealing contact between stud 155 and slide plate 162 thus being less than 10 square millimeters. The minimal seal area made possible by the valving structure of the invention provides low frictional resistance in operation and facilitates rapid valve operation, as well as reducing requirements for precision fitted or milled valve surfaces.

The valve 100 provides further advantages in that operation between charging, sealing and discharging modes requires few moving parts, the required motion of the moving parts being in a single plane. In the first described embodiment the spider 106 moves in the plane of lines 50, 60 while in the second and third abovedescribed embodiments motion of the spring arms 128, 129 or block 160 is in a plane transverse, and preferably normal to the plane of lines 50, 60. The motion required can be easily limited to short distances, for example, from one, to three, to six times the diameter of micropipet 210, or lines 50, 60. In contrast to syringe metering devices, the degree of motion in the valve 100 is independent of the volume of liquid pipetted. In contrast to pipetting devices employing conventional stopcocks, the valve 100 of the invention requires relative motion of sealingly engaged surfaces at no more than a single slidable sealed planar interface, e.g., the interface of stud 155 and slide plate 162.

From the foregoing description it will be apparent that valve 100 is adapted to divide a charged liquid into two continuous portions by mechanical separation of the fluid at single location. While the valve 100 can be modified to separate fluid at a plurality of locations, mechanical separation at but a single location in the fluid stream provides significant advantages in pipetting of volatile liquids. Since the pre-wash portion 47 is continuously exposed to the action of the suction means employed, vaporization of the pre-wash portion of liquid 47 creates no back pressure against any releasable seal formed by the valve 100. Mechanical separation of the pipetted liquid 44 in valve 100 also eliminates head space within pipet 36 and micropipet 210, reducing the hazard of premature discharge brought about by vapor pressure of the pipetted liquid. The pipetting apparatus 30 of the invention can be employed in pipetting volatile liquids such as ether which cannot be handled in many conventional automatic pipets.

3. THE PIPET-RETAINING MEANS AND PIPETS

The pipet-receiving portion 34 of pipettor 32 defines the pipet-receiving socket 202 which is adapted to receive the pipettor-engaging end 35 of a pipet 36 and guide the same into sealing engagement with gasket 200. In the embodiment of FIG. 4, socket 202 has the form of a cylindrical bore in pipet-receiving portion 34, and generally conforms to the cylindrical end 35 of pipet 36. A trigger-like pipet retaining member 300 is pivotally mounted on pipettor 32 and biased toward pipet gripping engagement of a pipet 36 between a pipet-gripping portion 302 of member 300 and an opposed wall portion of cylindrical socket 202. Pipets 36 of the same or different volumes can be interchangeably engaged with the pipettor 32 by applying manual pressure on release trigger 40 to displace the pipet gripping portion 302 of member 300 from socket 202. The pipet 36 can be withdrawn from socket 202 manually or allowed to slide free of its own weight to be replaced with another pipet 36.

The pipet or pipets 36 employed with the pipettor 32 in the embodiment of FIG. 4 are generally tubes of transparent, dimensionally stable and chemically inert material such as glass, having a tapered tip 236 through which liquids are charged and discharged, and are of generally circular cross-section as in conventional pipets. However, the pipets 36 of the invention each have a pipet-engaging portion 35 of predetermined outside diameter and length adapted to fit within the socket 202 of a pipettor 32. Portion 35 of each pipet 36 terminates in a smooth, flat sealing face 235 adapted to be sealed against gasket 200 about micropipet 210. The pipets 36 of the invention are calibrated to deliver and contain a predetermined volume between the tip 236 and sealing face 235, and include indicia 238 in standard volumetric units to indicate the total volume to be delivered by the pipet 36 when employed in conjunction with the pipettor 32. Indicia 238 thus can indicate a volume different from the internal volume of the pipet 36 between the tip 236 and sealing face 235 thereof, the difference between the indicated volume and the pipet volume corresponding to the volume of the micropipet 210 of the pipettor 32.

Referring more particularly to FIGS. 20–23, a preferred pipet 36 has indicia 238, tip 236, sealing face 235 and pipettor-engaging portion 35 as in the above-described embodiment. The pipettor-engaging portion 35 of pipet 36 also includes a circumferential collar

240 extending outwardly from the pipet 36 a predetermined distance from the sealing face 235, and a frusto-conical beveled end portion 242 surrounding sealing face 235. Collar 240 can be integrally formed of the same material as the pipet, or it can be fabricated separately and secured to the pipet 36. In a larger volume pipet 36 which includes an enlarged portion of increased cross-sectional diameter, the enlarged portion will be intermediate the collar 240 and the tip 236.

The pipet-receiving portion 34 of a pipettor 36 includes a socket 202, and gasket 200 surrounding micropipet 210. The socket 202 comprises an inner cylindrical portion 248 adapted to receive an end portion 242 and sealing face 235 of a pipet 36 and guide the pipet 36 toward sealing engagement of sealing face 235 with gasket 202 so that micropipet 210 communicates with the interior of the pipet 36. Socket 202 further includes a flared frusto-conical portion 250 which comprises an outwardly flaring extension of the inner cylindrical socket portion 248. The pipet-receiving portion 34 of pipettor 36 includes a narrow lip 252 at the periphery of the flared socket portion 250. The lip 252 is adapted to slide under the face 235 of a pipet 36 resting horizontally on a flat surface, so that lip 252 can slide along beveled end portion 242, guiding pipet portion 35 into flared socket portion 250. The pipet 36 and pipet receiving portion 34 of pipettor 32 thus coact to enable a user to engage a pipet 36 which is resting horizontally on a counter top or in a drawer, for example, in a one-handed scooping motion, utilizing pipet-receiving portion 34 as a scoop.

Also mounted on the pipettor 36 are a pipet retaining member 300 pivotally mounted by means of pivot pin 306, and a hand graspable release trigger 40, pivotally mounted on pipettor 36 by pivot pin 307. Retaining member 300 and trigger 40 are mechanically linked by connecting rod 308 and pivot pins 309. Retaining member 300 includes a pair of fork arms 310 adapted to receive the cylindrical pipet engaging portion 35 of a pipet, and a partially conical pocket 312 adapted to nestingly receive the collar 240 of a pipet 36 and support the pipet by collar 240. Retaining member 300 is normally biased toward a pipet-retaining position shown in FIG. 22 by conventional biasing means, e.g. spring 314. In such position fork arms 310 extend at least partially across flared portion 250 of socket 202, with the pocket 312 centered along the axis of socket 202 and opposed to gasket 200 and micropipet 210. The retaining member 300 is spaced from gasket 200 a distance preferably slightly less than the predetermined length of the pipets 36 from collar 240 to sealing face 235, so that the sealing face 235 of the pipet 36 is urged into firm sealing contact with gasket 200 by the nesting engagement between the pipet collar 240 and retaining member pocket 312. The bias provided by spring 314, trigger 40 and rod 308 is sufficient to maintain sealing pressure of pipet sealing face 235 against gasket 200 regardless of the orientation of the device, the volume and weight of the pipet 36 or whether or not the pipet 36 is filled with liquid. The inner lip 252 of flared socket portion 250 can include a rigid retainer stop 320 adapted to limit movement of retaining position. The stop 320 limits movement of retaining member 300 and a pipet 36 engaged thereby beyond a position in which undesirable deformation of gasket 200 can occur under pressure of the sealing face 235 of a pipet 36, while permitting sufficient movement toward the gasket 200 and sufficient deformation thereof to ensure sealing of the pipet 36 and gasket 200. Since stop 320 is adapted to limit the deformation of gasket 200 beyond a predetermined maximum, the bias provided by spring 314 can, if desired, be far in excess of that required to seal a heavy pipet 36. In ordinary usage, the pipets 36 are sufficiently similar in weight and gasket 200 has sufficient dimensional stability so that the precise placement of stop 320 is not critical. Stop 320 may generally be omitted if desired.

Retaining member 300 is pivotally movable (by manual pressure on trigger 40, for example) with respect to socket 200 between the retaining position of FIG. 22 to a pick-up position of FIG. 20. In the pick-up position the fork arms 310 and pocket 312 are displaced from the flared socket portion 250 a distance sufficient to permit free placement of a pipet 36 between fork arms 210 and nesting of pipet collar 240 in pocket 312, or permitting the pipet 36 to be disengaged from the retaining member 300, for example, to be replaced by another pipet 36.

In operation, manual pressure is applied to trigger 40 to move retaining member 300 to the pick-up position of FIG. 20. A pipet 36 is then positioned between fork arms 310 with the collar 240 nested in pocket 312, for example, by manually seating the pipet 36 or by moving the pipettor 32 toward a pipet 36 standing vertically in a pipet rack (not shown) to engage the pipet 36 between fork arms 310. When trigger 40 is released, retaining member 300 rotates on pin 306 toward socket 202, inserting portion 35 of pipet 36 into socket 202. As shown in FIG. 21, the beveled end portion 242 of pipet 36 can slide along the wall of flared socket portion 250 into cylindrical socket portion 248 as the retaining member 300 moves. Pipet collar 240 is free to tilt pivotally in pocket 312 as the pipet sealing face 235 is guided toward gasket 200 by the sliding engagement of pipet portion 35 and beveled portion 242 against the walls of socket 202. When the retaining member 300 reaches the pipet-retaining position illustrated in FIG. 22, further motion is prevented by sealing engagement of pipet sealing face 235 with gasket 200 surrounding micropipet 210 or by stop 320, when employed. Cylindrical socket portion 248 need not be of the same diameter of the pipet 36, so long as it is adapted to guide the pipet sealing face 235 into sealing engagement with gasket 200 so that the micropipet 210 communicates with the interior of the pipet 36.

The pipettor 32 and pipets 36 of the invention can thus operate to pick up, engage and disengage pipets 36 without requiring manual handling of the pipets 36 themselves. The freely-movable nature of the pipettor 32 and the cooperative structural elements of the pipet engaging portion 34, retaining member 300 and the pipets 36 themselves facilitate pick up, engagement and operative sealing of pipets 36 from the two positions most frequently encountered in laboratory pipetting, that is, horizontal position of pipets 36 lying on a counter top or in a drawer, for example, or the vertical position of a pipet 36 in a rack.

4. MEANS FOR OPERATING VALVE 100

Both the first and third above-described valve embodiments are controlled by means of a push rod 170, connecting a rotatable element of the valve 100 to a control lever 172 and control button 38 movably mounted on the pipettor 32. Lever 172, as illustrated in FIG. 6 is pivotally mounted with pipettor 32 on a shaft 190, mounted in the pipettor and extending through a slot 192 in lever 172. Mounting of lever 172 on shaft 191 also includes means for biasing the lever 172 outwardly from shaft 191, e.g., spring 176. The opposed end of lever 172 extends through a slot 191 in the pipettor body 132, terminating in button 38. The inner surface of pipettor body 132 along the sides of slot 191 defines a track 175. Lever 172 includes an outwardly projecting rod 174 on each side thereof, rod 174 being adapted to move slidingly along track 175, and being normally biased toward sliding contact with track 175 by the action of spring 176. Slot 191 is bounded at opposed ends thereof by a forward or charge-position stop 177 and a rearward or discharge-position stop 179, stops 177 and 179 comprising portions of pipettor body 132 at the forward and rearward boundaries of slot 191. Stops 177 and 179 correspond to the positions of rod 174 and control lever 172 when the valve 100 is in the charging or discharging modes, respectively. Intermediate stops 177 and 179, track 175 includes a notch 178 adapted to receive rod 174 when the lever and rod 172, 174 are in a position corresponding to the sealing mode of valve 100. By means of notch 178, positive locking of lever 172 in a valve-sealing position is obtained by sliding the rod 174 along track 175 until rod 174 is seated in notch 178 under the urging of spring 176. Such positive locking of control lever 172 ensures against accidental charging or discharging as well as indicating to an operator when control button 38 has been moved sufficiently to put valve 100 in the pipet-sealing mode. The control button 38 and lever 172 can be moved manually to provide partial opening of either the suction or discharge lines 50, 60 in valve 100 when immediate manual control of the charging or discharging rate is desired. Inadvertent movement of the valve 100 beyond a charging or discharging position is prevented by stops 177, 179. As illustrated in FIG. 23, the pipettor 32 includes a valve 100, micropipet 210, gasket 200, socket 202, retaining member 300, suction and pressure lines 50, 60 and valve control button 38, control lever 172 and connecting rod 170 substantially similar to those of the embodiment described above. In the embodiment of FIG. 23, control lever 172 includes an outwardly projecting rod 174 which under the bias of spring 176 rides in a track 175 internally of the pipettor body 132. Rod 174 is adapted to slide along track 175 between a forward charge-position stop 177 and a rearward discharge-position stop 179, substantially as described with respect to the embodiment of FIG. 6. Track 175 has a concave curvature extending from stops 177, 179 toward notch 178 and outwardly from shaft 191 so that rod 174 is normally biased by spring 176 for cam-like, sliding movement along track 175 to a valve-sealing position. Rod 174 can be disengaged from notch 178 by manual pressure on control button 38 permitting manual movement of button 38 and lever 172 toward a discharging position or a charging position. Upon release of control button 38, lever 172 is returned to the valve sealing position by the biasing action of spring 176 and cam-like engagement of rod 174 and track 175. Such control means provide automatic return to a valve sealing position upon release of control button 38 whether or not release is intentional.

The pipettor 32 of FIG. 23 can also include electrical valve control means and a further modification of pipet 36. As shown in FIG. 23, the pipet 36 includes a tip 236, collar 240, sealing face 235, and indicia 238 as described above with respect to other embodiments thereof. In addition, pipet 36 carries a strip 250 of electrically conductive material such as steel, brass, copper, silver or the like extending about the collar 240 and along the exterior of pipet 36 to the tip 236. The socket 312 of retaining member 300 includes a surface of similarly conducting material, e.g., contact 252 which is connected via a lead 254 housed within member 300 and the pipettor 32 to a source of electric current. The valve 100 includes an electrically conductive contact in the suction line 50, e.g., an electrically conductive suction line coupler 256 of silver, stainless steel, brass or the like, in the suction line 50. Coupler 256 is connected via lead 258, solenoid 260 and lead 262 to a source of current. With a pipet 36 operatively engaged in the pipettor 32, lead 254, contact 252, strip 250 and coupler 256, lines 258 and 262 and solenoid 260 define an open electric circuit adapted to operate the solenoid 260 upon closing the circuit between strip 250 at the pipet tip 236 and the suction line coupler 256. When pipet tip 236 is immersed in a liquid electrolyte 44 to be pipetted, for example, from a test tube 264, and valve 100 is in the charging mode, the normally open circuit between pipet tip 236 and coupler 256 will be closed by the liquid electrolyte 44 charged into pipet 36, micropipet 210 and suction line 50 to coupler 256. The closed circuit, and resulting operation of the solenoid 260 thus serves as means for electrically sensing completion of charging. Audible or visible signal means such as a buzzer or indicator light can be employed in the circuit in lieu of or in addition to solenoid 260.

In addition, control lever 172 can include a second outwardly projecting rod 180 adapted to ride along an opposed track 185 defined by surface of a catch lever 182 facing track 175. Catch lever 182 is pivotally mounted to pipettor body 132 on an internal flange 183. Track 185 and catch lever 182 are normally biased toward sliding engagement with rod 180 by solenoid spring 261, when the solenoid 260 is not activated by a current. A step or catch 186 is included in track 185 to receive rod 180 when control lever 172 is in the forward or charging position. Catch 186 is adapted to retain rod 180 and thereby control lever 172 in such position against the bias of spring 176, track 175 and rod 174 in the absence of manual pressure on button 38 or activation of the solenoid 260. In operation, control button 38 is manually pushed to the charging position and released, the control button 38 and lever 172 being maintained in the charging position by rod 180 and catch 186. During charging liquid electrolyte 44 is drawn into pipet 36, micropipet 210 and into suction line 50 to contact the coupler 256, closing the electrical circuit through lead 254, contact 252, strip 250, coupler 256, leads 258 and 262 and the solenoid 260,

and activating the solenoid **260**. When solenoid **260** is activated, lever **182** is pivotally moved clockwise with respect to FIG. **23**, disengaging the catch **186** from rod **180** and permitting control lever **172** to return to the valve sealing position. The solenoid-actuated return of control lever **172** operates valve **100** via connecting rod **170**, thus dividing the liquid **44** in pipet **36** and micropipet **210** from the pre-wash portion of liquid in the suction line **50** and opening the solenoid circuit, allowing lever **182** to return to a position in which track **185** again engages rod **180**. It will be seen that the embodiment of FIG. **23** further reduces the need for operator attentiveness and permits automatic limitation of the amount of liquid **44** to be employed in pre-washing micropipet **210** and valve **100**.

OPERATION OF THE INTEGRATED APPARATUS

In pipetting operations carried out with the apparatus **30** of the invention, the pipet-driving subassembly **80** is activated, as by making the appropriate connections to source of power and closing switch **41**, to supply pressure and suction in tubes **65**, **55** and pressure and suction lines **60**, **50** in the pipettor **32**. The pipettor **32** is grasped with the operator's hand **25** about handgrip **37**, lifted from its receptacle **39** in housing **28**, and moved to a desired position, limited only by the length of tubes **55**, **65**. A pipet **36** of the desired volume is selected, trigger **40** is depressed manually, and the pipettor engaging end **35** of the pipet **36** is inserted into socket **202**. Trigger **40** is released, the pipet **36** being then operably engaged with the pipettor **32** by means of the retainer **300** and gasket **200**. The pipet tip **236** is lowered into a liquid **44** to be pipetted, e.g. from beaker **45**, and control button **38** is moved to the charging position (or in the embodiment of FIGS. **4** and **5**, control button **138** is depressed) and the pipet **36** is charged. Since the pipet **36** will typically contain air prior to charging, the initial phases of charging provide air washing of micropipet **210**, valve **100** and suction line **50**.

After charging is complete the control means are operated to put valve **100** in the sealing mode and the charged pipet **36**, liquid **44** and pipettor **32** are moved as may be desired to dispose pipet tip **236** within or above a beaker **46**, or tube or the like into which the pipetted liquid is to be discharged. The appropriate control means, button **38** or pressure control button **139**, are operated to put valve **100** in the discharging mode to discharge the liquid **44**. As the pressurized discharge fluid (air or inert liquid) enters pipet **36**, the valve **100** and micropipet are washed by the discharge fluid. After discharging is complete, the cycle can be repeated, utilizing the apparatus as a repetitive dispenser. Alternately, valve **100** can be operated to the sealing mode again, and the pipet **36** can be disengaged from the pipettor **32** and replaced by another pipet **36**. In ordinary use it is desirable to provide a plurality of standardized pipets **36** having similar sealing faces **235**, beveled ends **242** and collars **240**, but adapted to pipet different predetermined volumes, for example, 0.1, 1, 2, 5, 10, 15 milliliters and so on, the number of pipets **36** of each volume being selected according to the operator's needs. In a typical analytical procedure, a single pipetting apparatus **30** may be used with several similar pipets **36** in succession to pipet several different 0.1 milliliter aliquots of several serum samples into a series of test tubes, and then employed directly with a single larger pipet **36** to pipet 5 milliliters of biuret reagent into each tube for analyses of protein by the biuret reaction. In most cases, the washing of micropipet **210** and valve **100** during the pipetting operation is sufficient to permit pipetting a series of different successive liquids with little or no detectable interference between liquid samples. Interference can be further reduced by employing a clean pipet for each liquid sample; also, the pipettor **32** can be rapidly cleaned or rinsed, when necessary or desirable, without disassembly of valve **100**. During a typical series of pipetting operations, the trap **85** is emptied from time to time as may be needed, for example, to prevent over-filling or accumulation of mutually incompatible materials in the trap **85**.

Various modifications can be made in the pipetting apparatus **30**. For example, the trigger grip **40**, fork arms **310** and pocket **312** of the retaining means can all be included in a retaining member **300** of unitary construction as illustrated in FIG. **6**. The walls of cylindrical and flared portions **248**, **250** of socket **202** can be of glass or transparent plastic such as polystyrene or an acrylic resin or can include a transparent section, view port or the like to permit visual observation of the seating of a pipet **36** against gasket **200**. In another modification each pipet **36** can be provided with its own gasket **200**. In the pipet-driving subassembly **80**, various means can be employed to sense the liquid level in the trap **85** and interrupt operation of the suction and pressure structure automatically when the liquid level in the trap **85** reaches a pre-determined height. Liquid level sensing means in trap can also be employed with an indicator light, buzzer or the like to signal the operator that the trap **85** should be emptied. Where mobility is not required, the pipettor **32** and driving subassembly **80** can be secured together by appropriate mounting means, and appropriate means can be employed to operate valve **100** by electrical means employing solenoids, electric motors or the like or mechanical means such as described in my application Ser. No. 860,775, filed Sept. 24, 1969.

In summary, it will be seen that the apparatus of the invention provides a highly versatile and simple means for pipetting of fluids. While certain embodiments and variations of the invention have been described, a number of further variations and modifications can be made therein. For example, the pipet retaining means can be modified to include a second valve, socket and gasket to permit charging and discharging to be accomplished through appropriate lines via the additional valve in modifications similar to those described in my copending application, Ser. No. 860,775, filed Sept. 24, 1969. A plurality of pipets can be employed with a plurality of valves and additional lines to provide for simultaneous charging of all the pipets and discharge through successive ones of the pipets to a point of use. The use of a plurality of valves, lines and pipets can also be employed to provide for discharging of one pipet simultaneously with charging of another, as may be desired. Consequently, it will be seen that the invention is not limited to those embodiments specifically described above in detail.

What is claimed is:

1. Pipetting apparatus adapted for use with a plurality of interchangeable pipets, the apparatus com-prising a pipettor; means on the pipettor for selectively operatively engaging a pipet, said means including a micropipet in the pipettor adapted to communicate with a pipet operatively engaged therewith and gasket means for releaseably engaging an end portion of a pipet to provide sealingly communicative engagement of the pipet and micropipet; a hollow suction line in the pipettor; a hollow pressure line in the pipettor; valve means in the pipettor for providing selective communication and sealing between the suction and pressure lines and the micropipet, the valve means being operable between a charging mode in which the micropipet communicates with the suction line and is sealed from the pressure line, a sealing mode in which the micropipet is sealed from communication with both lines whereby a predetermined volume of fluid in the micropipet and a pipet engaged therewith is separated from communication with the suction line, and a discharging mode wherein the micropipet is sealed from the suction line and communicates with the pressure line; means for coupling the suction line to a source of suction adapted to draw a column of fluid through the micropipet and a pipet engaged therewith and into the suction line when the valve means is in the charging mode; means for coupling the pressure line to a source of fluid pressure adapted to provide pressure in the pressure line for discharging the micropipet when the valve is in the discharging mode.

2. Apparatus of claim 1 wherein the valve means is adapted to mechanically divide a fluid column which has been drawn into the micropipet and suction line during the charging mode into an integral fluid portion of predetermined volume enclosed by the micropipet and a pipet engaged therewith and a second integral fluid portion within the suction line, the valve means being adapted to divide the fluid column at a single location within the valve.

3. Apparatus of claim 1 further comprising manually operable means on the pipettor for disposing the valve means in a selected mode, and means for indicating the movement of a liquid column beyond the micropipet.

4. Apparatus of claim 3 wherein the indicating means comprise a transparent wall portion of the suction line to permit visual observation of a liquid column moving therethrough and a fluid resistance in the suction line adapted to impede the flow rate of such liquid column a predetermined distance along the suction line downstream of the valve.

5. Apparatus of claim 3 wherein the indicating means includes an electrical contact in the suction line and electrically conductive leads on the pipettor and on a pipet engaged therewith adapted to contact a liquid electrolyte to be pipetted, the indicator means being responsive to an electrical circuit through a column of the liquid electrolyte drawn into the suction line to the contact for sensing the completion of charging.

6. Apparatus of claim 5 further comprising biasing means in the pipettor for normally biasing the valve means toward the sealing mode, locking means for releaseably maintaining the valve means in the charging mode, and means responsive to an electric current conducted by a liquid electrolyte column through the valve means, micropipet and a pipet engaged therewith for releasing the locking means.

7. Apparatus of claim 1 wherein the valve means comprises a valve base mounted in the pipettor and having a bore therethrough, portions of the base surrounding the bore defining wall portions of the micropipet; and a valve block having separate bores therethrough, portions of the block surrounding the bores defining wall portions of the suction line and pressure line, said wall portions being selectively sealably engageable with the wall portions of the micropipet, means for mounting the valve block for movement relative to the valve base, and means for moving the valve block relative to the valve base between relative positions in which the micropipet communicates with one of said lines and is sealed from communication with the other of said lines, and a position in which the micropipet is sealed from communication with both lines by sealing engagement of wall portions of the micropipet with the valve block.

8. Apparatus of claim 7 wherein the valve base includes a hollow stud surrounding the micropipet and defining a wall portion thereof, the stud extending beyond a face of the valve base toward the valve block, the stud terminating in a sealing face adapted to sealingly engage a portion of a face of the valve block to provide sealing communication between the micropipet and a single one of said lines, and means including said stud for maintaining a major proportion of the opposed faces of the base and block spaced from each other to permit one of said lines to communicate with atmosphere between the opposed spaced faces when said line is sealed from communication with the micropipet.

9. Apparatus of claim 8 wherein the portions of the micropipet, suction line and pressure line at the opposed faces of the block and base are substantially cylindrical and having substantially similar diameters and substantially parallel axes; and wherein the valve block is mounted for relative movement in a plane substantially normal to the axes of the micropipet and lines.

10. Apparatus of claim 8 wherein the portions of the micropipet, suction line and pressure line at the opposed faces of the block and base are substantially cylindrical and having substantially similar diameters, wherein the sealing face of the stud extends radially outwardly from the micropipet a distance of between one and two times the diameter of the micropipet, and wherein the suction and pressure lines are spaced sufficiently from each other to prevent simultaneous sealing of both lines when the sealing face of the stud is sealingly engaged with a portion of the block face intermediate the suction and pressure lines.

11. Pipetting apparatus comprising:

pipet operating means including a pipettor;

suction means for providing pipet-charging suction to the pipettor;

pressure means for providing pipet-discharging pressure to the pipettor;

hollow suction and pressure lines in the pipettor adapted to apply suction and pressure to a pipet;

means including suction and pressure connecting tubes for providing communication between the suction and pressure lines and the corresponding suction and pressure means while permitting movement of the pipettor relative to the suction and pressure means;

sealing means on the pipettor for operatively engaging an end of a pipet; and

valving means on the pipettor for selectively charging a fluid into a pipet engaged by the sealing means and partially through such pipet into the suction line, selectively dividing fluid so charged into a continuous pipetted portion in the pipet and a single continuous fluid portion in the suction line, and selectively discharging the pipetted fluid portion under pressure from the pressure line, said valving means including a valve base having a cylindrical micropipet bore therein adapted to communicate with a pipet engaged by the sealing means; a valve block having cyclindrical suction and pressure line bores therein, the axes of said bores being parallel to the axis of the micropipet bore, means including wall portions of said parallel bores at a planar interface of the valve base and valve block for sealing a selected line bore in communication with said micropipet bore; means for movably mounting the valve block for limited motion relative to the base in a plane transverse to the parallel axes of the bores between a position in which a selected one of said line bores sealingly communicates with the micropipet bore and a position in which the micropipet bore is sealed; and means on the pipettor operably engaged with the valve means for selectively moving the block relative to the base.

12. Apparatus of claim 11 wherein the suction connecting tube includes a portion which is wettable by the fluid.

13. Apparatus of claim 11 further comprising a fluid resistance in the suction line upstream of the valving means, said fluid resistance being adapted to impede the flow of liquid along the suction line.

14. Apparatus of claim 11 wherein the suction means and pressure means include the intake and exhaust of a single pump, said pump being adapted to operate independently of the operation of the valving means, and wherein the valving means includes means for selectively venting the suction line and pressure line when said lines are sealed from communication with a pipet.

15. Apparatus of claim 11 further comprising means operable independently of the suction means, pressure means and valve means for selectively regulating the pressure in the pressure line and means for independently regulating the suction in the suction line.

16. The apparatus of claim 11 wherein the valving means includes wall portions of the micropipet bore extending beyond the base toward the block and terminating in a planar face slidably sealingly engaged against a planar face of the block which includes wall portions of the parallel suction and pressure lines.

17. The apparatus of claim 16 wherein the valving means further includes means for limiting the relative planar motion of the base and block to a distance between about one and about six times the diameter of the micropipet bore.

18. In a pipetting apparatus comprising means for engaging a pipet to be employed in pipetting a liquid, means including a valve for selectively charging liquid into a pipet by suction, sealing liquid so charged in the pipet and discharging liquid from the pipet under pressure, the pipet having a sealing and face adapted to releaseably sealingly engage the pipettor and an opposed pipet tip through which pipetted liquid is to be charged and discharged, the improvement wherein the pipet includes an outwardly-extending collar a predetermined distance from the sealing end face thereof, wherein the apparatus further comprises a pipet-retaining member including a pair of fork arms adapted to receive a portion of the pipet intermediate the collar and tip between the fork arms, the fork arms being adapted to engage the pipet collar, the fork arms being mounted on the apparatus for movement of the fork arms relative to the pipet engaging means between a first position in which the fork arms and pipet-engaging means are in pipet-retaining relation to each other and a second pipet-releasing position in which the fork arms are displaced from the pipet-engaging means.

19. Apparatus of claim 18 wherein the apparatus includes a pipet-receiving socket adapted to slidably engage a portion of a pipet and guide the sealing face of the pipet toward engagement with the pipet-engaging means during motion of the fork arms toward the first position thereof.

20. Apparatus of claim 18 wherein the apparatus includes a pipet-receiving socket adapted to slidably engage a pipet and guide the sealing face thereof toward engagement with the pipet-engaging means, the socket having a peripheral lip adapted to slidably engage a corresponding end portion of a pipet to guide the sealing face into the socket.

21. Apparatus of claim 20 wherein the pipet engaging means includes a micropipet adapted to communicate with the interior of the pipet and a gasket surrounding the micropipet adapted to engage the sealing face of the pipet, and wherein the socket includes an inner portion adapted to guide the sealing face into sealing engagement with the gasket so that the micropipet communicates with the interior of the pipet, and an outer flared socket portion adapted to slidably engage an end portion of the pipet and guide the sealing face thereof into guiding engagement with the inner socket portion.

22. A pipet comprising a tubular body having, at opposed ends of the body, a pipet tip and a sealing face adapted to be releaseably sealingly engaged with a pipettor; the pipet being adapted to contain a predetermined volume of fluid between the tip and sealing face; and a collar extending outwardly from the pipet body, the collar being disposed on the pipet body intermediate the ends thereof and a predetermined distance from the sealing face thereof, the collar being adapted to be nestingly engaged by a corresponding portion of a pipet-retaining member on a pipettor.

23. A pipet of claim 22 further comprising electrically conductive means on the exterior of the pipet for conducting an electric current between the pipet tip and an electrical contact on a pipettor.

24. A pipet of claim 22 wherein the pipet body includes a beveled end portion at the sealing face, the beveled end portion extending about the sealing face and being adapted to slidably engage a wall of a pipet-receiving socket in a pipettor.

25. A pipet of claim 24 further comprising indicia disposed on the pipet body, said indicia being in standard volumetric units and indicating a volume corresponding to the predetermined internal volume of the pipet between the tip and sealing face thereof.

26. A pipet of claim 25 wherein the indicia on the pipet indicate a volume greater than the total internal volume of the pipet by a predetermined volumetric increment corresponding to the volume of a micropipet of a pipettor which is adapted to operatively engage the pipet, said volumetric increment being a minor proportion of the total internal volume of the pipet.

27. A method useful for pipetting, the method comprising:

a. coupling a pipet to a tubular suction line having a moveable wall and a tubular pressure line having a moveable wall to form a selective three-way intersection of the pipet with the lines;

b. applying fluid suction in the suction line;

c. continuously applying fluid pressure in the pressure line;

d. charging the pipet, including moving selected wall portions of the pressure line to seal said line from the intersection, moving selected wall portions of the suction line to provide communication between the suction line and the pipet, and drawing a liquid to be measured into the pipet and partially therethrough into the suction line;

e. thereafter moving selected wall portions of the suction line to seal between the suction line and the intersection, thereby dividing the portion of liquid drawn into the suction line from the portion remaining in the pipet, said wall portions being moved to provide the seal at a single location in the line; and

f. thereafter moving the selected wall portions of the pressure line to provide communication between the pressure line and the intersection.

28. The method of claim 27 wherein the moveable walls of the suction and pressure lines include relatively moveable opposed wall portions, and wherein the respective opposed wall portions are moved in a plane perpendicular to the axis of their respective line.

29. The method of claim 27 wherein the pipet is coupled to the lines releaseably coupling the pipet to a hollow tubular walled micropipet which selectively intersects said lines.

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