United States Patent

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[54] **LIQUID MIXING AND TRANSFER APPARATUS AND METHOD**
35 Claims, 7 Drawing Figs.

[52] U.S. Cl. 259/4
[51] Int. Cl. B01f 5/00
[50] Field of Search 68/183; 259/18, 4, 36, 60, 151, 147

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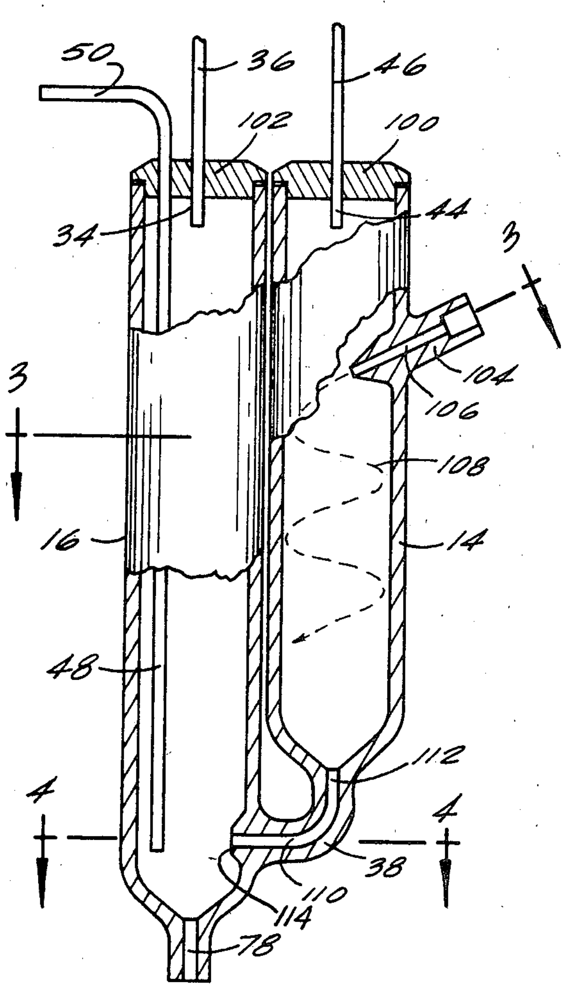
ABSTRACT: Apparatus comprising at least one vessel into which liquids are introduced, mixed and drained without the use of any mechanical mixing device, without contamination and without agitation to an extent that slow-rising or persistent bubbles will not form. Such apparatus is adapted for connection into a system for the continuous automatic processing of samples. The apparatus comprise a single or plurality of vessels performing the functions mentioned and have a fitting at least in one vessel arranged to introduce the liquids tangential to the inner wall of the receiving vessel to produce a helical downward swirling of the liquid to impart rotary motion thereto. At the same time, at least in single vessels, an up-and-down movement of the liquid is produced by the introduction of a gas into the drain and generates fast-rising bubbles passing through the liquid thoroughly to mix the same in the vessel. Alternate means for use in multiple vessel apparatus provide for interchange or transfer of liquids at the bottom of the vessels to effect the up-and-down mixing as well as rotation of the liquid. Structure for retaining liquid in the vessels by the use of gas introduced through a drain; for effecting liquid removal by gas pressure controlled to provide minimum agitation; and for other purposes are disclosed.

Methods for mixing and transferring liquids are described in connection with the apparatus of the invention, especially a method of expelling liquid from a vessel by the use of gas pressure above the surface of the liquid in which the amount of pressure decreases with the lowering of the level.



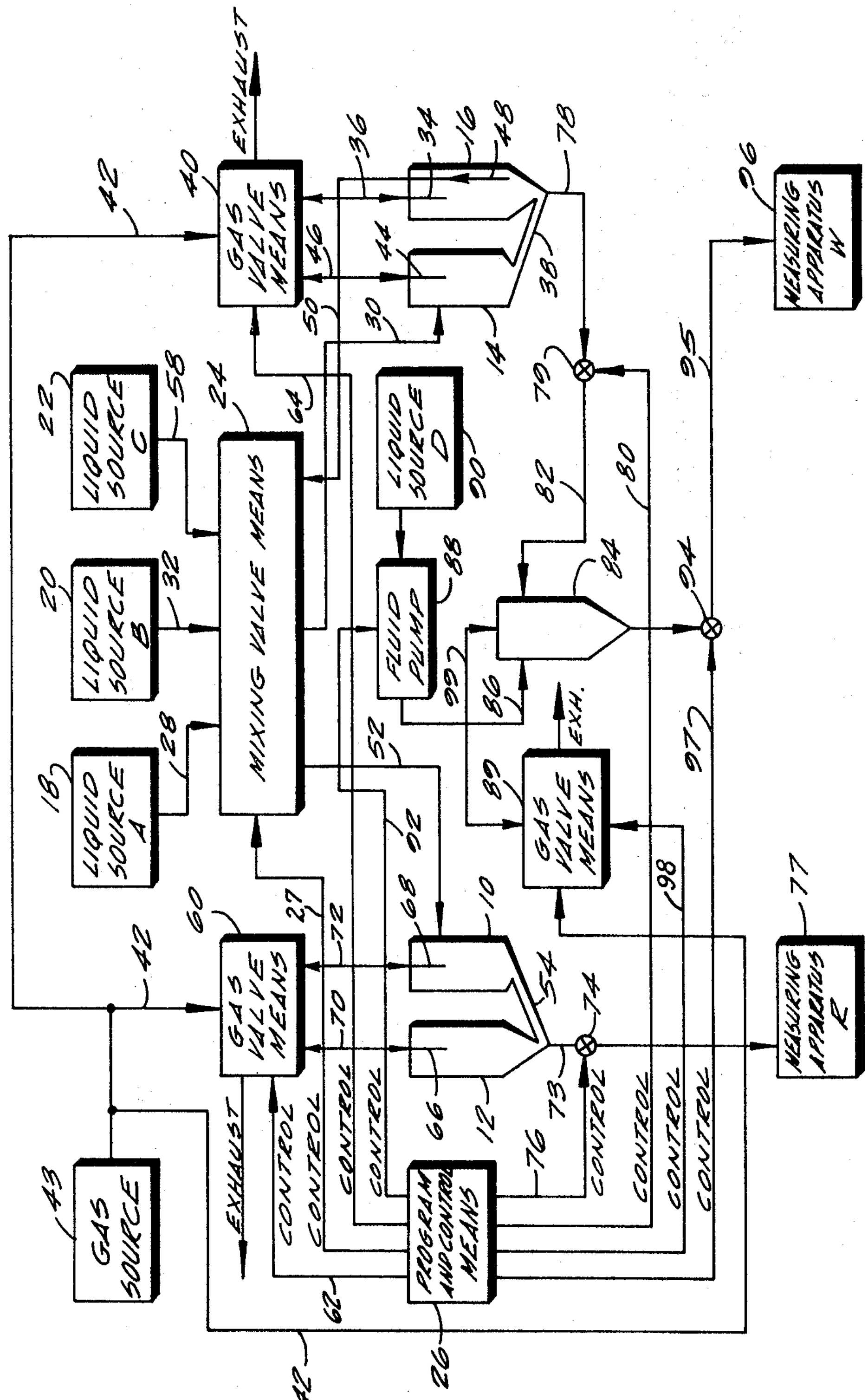


FIG. 1

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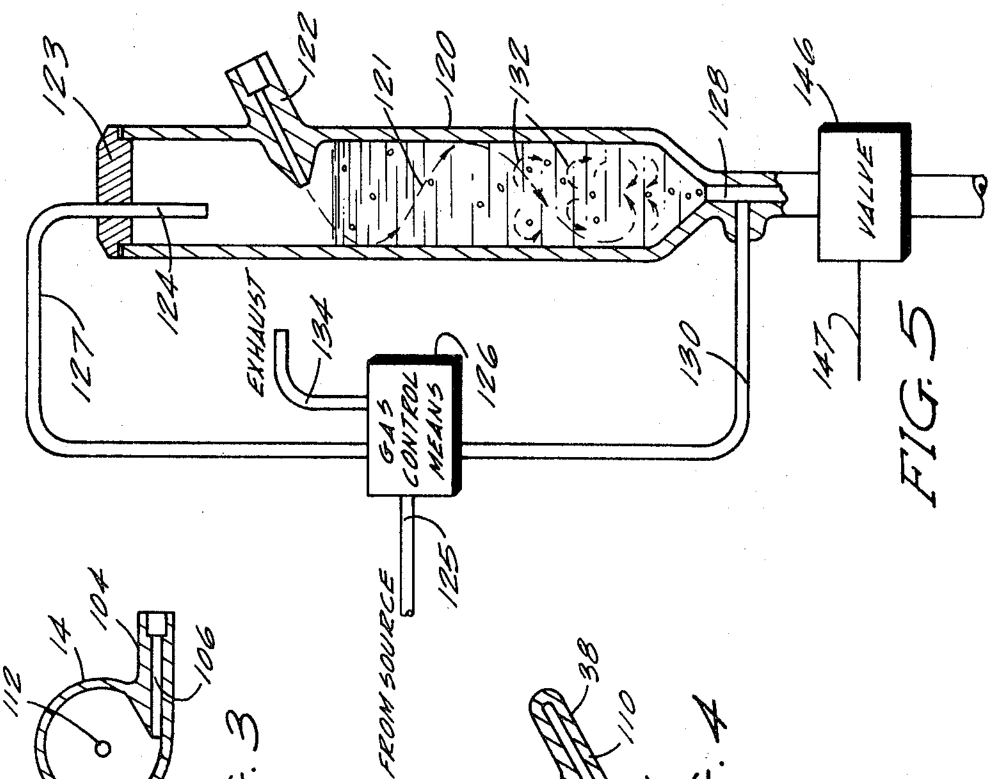

FIG. 5

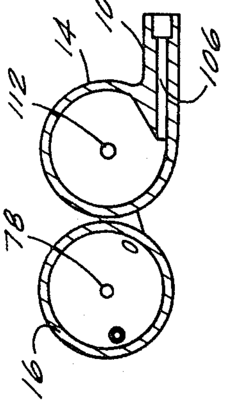

FIG. 3

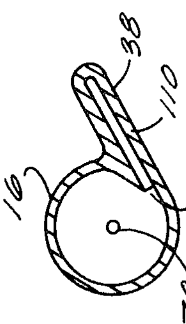

FIG. 4

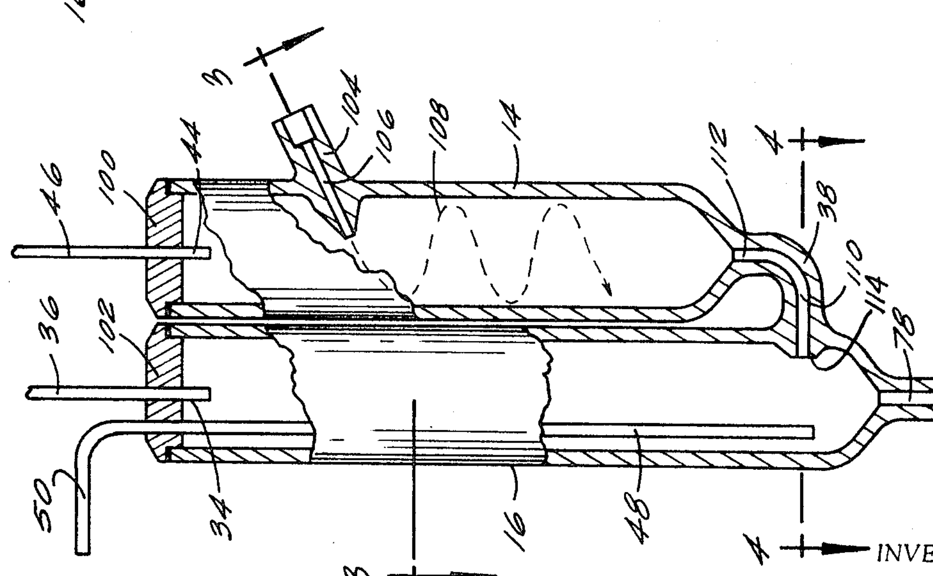

FIG. 2

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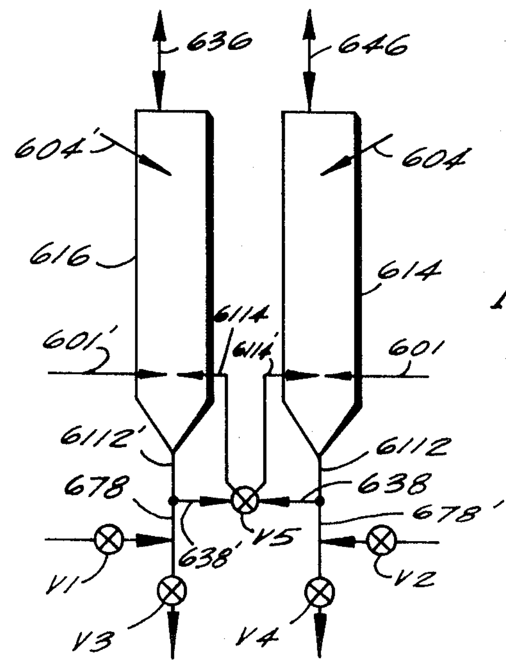

FIG. 6

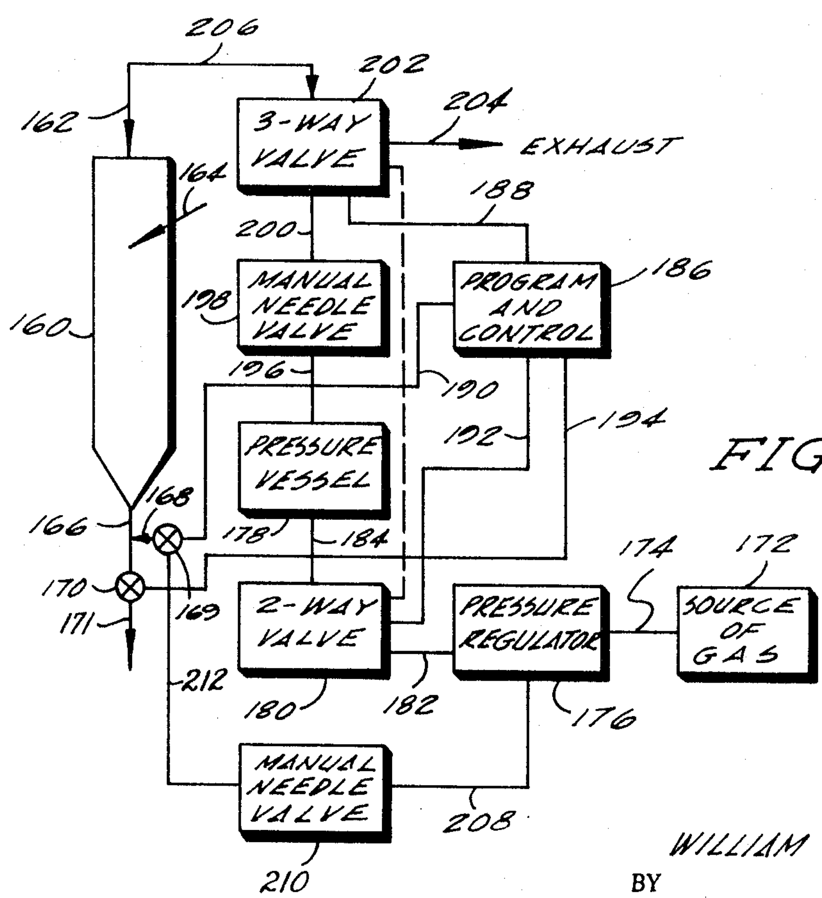

FIG. 7

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LIQUID MIXING AND TRANSFER APPARATUS AND METHOD

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of a copending application filed in the name of the applicant and Robert I. Klein, Ser. No. 631,284 on Apr. 17, 1967 entitled "AUTOMATIC APPARATUS FOR PROCESSING OF BLOOD OR THE LIKE TO OBTAIN CERTAIN PARAMETERS." The portion of the said copending application which is common with this application is the sole invention of the applicant therein.

BACKGROUND OF THE INVENTION

The field of the invention herein is the broad field which uses vessels and connecting conduits for the intermixing and the transfer of fluids primarily for the purpose of making measurements and tests on said fluids. It will be appreciated that this description is somewhat general, but the method and apparatus that are disclosed in this specification are capable of many uses. In medicine, biology, chemistry and allied fields, research as well as routine testing requires the use of apparatus which classically has been termed "glassware" or even "hardware." Test tubes, breakers, bottles, retorts, pipets, stills and a whole host of varied apparatus are quite well known and have been used for many years. Manual handling and manipulation of this type of apparatus is a technique learned early by those working in these fields.

In recent years the so-called automatic chemistry apparatus has become popular, especially where testing and measurements are to be done on a production basis, with many tests to be made and complex routines to be repeated over and over again, but with different samples. The copending application, which has been identified above, is of this type, and it is primarily intended for the measurement of parameters of blood. In that apparatus, samples of whole blood may be introduced at a rate approximating several samples per minute; and the apparatus performs the tests and computations needed for obtaining blood count of white and red cells, a hematocrit determination, a hemoglobin measurement, and so on. Other apparatuses are known which handle samples and make a plurality of tests and measurements automatically. Some of the patents which describe such apparatus are U.S. Pat. Nos. 3,038,340, 2,879,141 and many others. Such apparatuses are used in chemical analysis, chromatography, spectrophotometry, as well as in the measurement and analysis of biological specimens.

Automatic apparatus is required to draw in fluids, to dilute concentrates and mix liquids, In the case of blood sampling, multiple dilutions must be made, red cells must be lysed for making white cell determinations, liquids must be pumped, transferred, and moved between vessels. The manual techniques which are classically used in conventional work are not satisfactory, and obviously the vessels and equipment of the ordinary laboratory are not suitable for automated apparatus.

Accordingly, different forms of glassware have been developed to meet the demand for apparatus which operates automatically.

The basic requirements of automatic apparatus have produced problems which are believed not fully solved by the glassware which has thus far been developed. A review of these problems will be useful in pointing out the achievements of the invention herein and in emphasizing the importance of some of its aspects.

Probably the most important problem of all is the difficulty of handling a plurality of fluids on a continuous basis. Obviously, a continuous flow device would be the most satisfactory from an automatic machinery standpoint, so that the apparatus will keep repeating the same tests over and over again on the continuously flowing sample and give the answers. Unfortunately, the usefulness of such a device is manifestly limited. The worker must know the measurements or test results for each of a series of completely different samples. In the case where the apparatus of the copending application is used for blood sample measurements, the consecutive samples may comprise blood of widely different characteristics.

This means that the machine must handle each sample separately, and hence it is a batch device, but must be capable of routinely, quickly and continuously operating on sample after sample, giving the results accurately and without confusing the several samples. Accordingly, the problem arises of keeping the samples separate from one another, and this in turn requires absolute control of the handling of the samples. Especially there can be no contamination in an acceptable device. Inherent in the demands of such an apparatus is the need for accuracy in order that quantitative determinations be reliable.

The invention has as one of its important objects the provision of apparatus which enables simple and complete transfer of liquids from one vessel to another. This is the criterion of accuracy, and has as one of its concurrent benefits the minimum of contamination, for, if the transfer is complete and efficient, there will be no residuum to spoil the following sample.

In automatic apparatus, the worker rarely has the opportunity of handling or manipulating any of the apparatus manually. As a matter of fact, such an arrangement would be inconsistent with the concept of automation. Accordingly, he normally cannot follow each sample as it moves through the machine and must depend upon the machine to do everything that he could readily do in making a test in the classical method. The simple technique of carefully introducing a second liquid into a vessel containing a first liquid and gently intermixing them without violence becomes a complex task in a machine. The worker could readily perform the task manually by dexterity of his fingers and wrists, but unfortunately the automatic apparatus cannot have fingers or wrists.

According to the invention, an important object is the provision of structure which enables the introduction of liquids into vessels which already contain liquids or along with other liquids in a manner which results in a minimum of turbulence, but which enables the liquids to be intermixed while entering and additionally after entering.

Another object of the invention is concerned with the provision of means for accomplishing mixing and delaying the movement of liquid from a vessel simultaneously through the use of gas under pressure. By suitable arrangements in combination with the liquid vessels and conduits, the gas under pressure may be used for transferring liquid from one vessel to another or out of a vessel and for mixing fluids.

In the apparatus which is described in some detail in the above-described copending application, some of the tests which are conducted automatically include the use of the Coulter principle which is disclosed in U.S. Pat. No. 2,656,508. Red and white blood cells are scanned as they pass with liquid through an aperture of very small dimensions simultaneously with the passage of an electric current through such aperture. The scanning elements comprise the corundum wafers forming the passageways through which the liquids are forced. They are normally incapable of distinguishing between fine bubbles and particles, and hence in apparatus of the type where counting is to be done, it is most undesirable to have bubbles of any kind. Even optical counting can be rendered inaccurate by reason of the presence of bubbles. Where fluids are to be passed through pumps, bubbles produce inaccuracies because the entrapped gases are compressible although the liquids carrying the same are not.

Many types of bubbles produced by turbulence during introduction, intermixture, dilution, transfer and similar handling of fluids are transient and disappear quickly, but the trouble arises with those that persist. Many chemicals promote bubbles, such as, for example, lysing agents which are used to break up the red blood cells so that white cell measurements may be made. The invention is especially useful in such cases to prevent the formation of bubbles by the structures which will be described.

SUMMARY OF THE INVENTION

Generally, the objects of the invention are inferred from the above discussion, namely, to provide apparatus for fluid transfer, dilution, mixture and so on in a completely enclosed system without turbulence, the formation of objectionable bubbles and contamination from sample to sample.

Additional objects of the invention are to provide apparatus in which gas pressure is used to prevent liquid from leaving a vessel while at the same time serves to mix the same; in which gas pressure is used to cause the transfer of liquid from one vessel to another or is used to drain a vessel; in which gas pressure is controlled to produce a minimum of turbulence during these operations.

One specific object of the invention relates to the manner in which the gas is controlled, as, for example, in draining a vessel. While the major portion of the liquid remains in the vessel, the pressure of the gas above the liquid which is forcing the liquid out of the drain is at a maximum to speed the evacuation of the vessel. By suitable regulation means, the pressure of the gas is gradually lowered as the vessel empties, until at the last instant, the pressure is practically zero so that the draining occurs completely and yet without forcing gas through the drain to burst into the following receptacle for the fluid.

In the case of apparatus which enables introduction of liquids into vessels without turbulence and while mixing the same, the vessel comprises a cylindrical member having an inlet pipe or fitting in which the axis of the pipe at the point where it enters the vessel is tangential to the inner surface of the vessel and preferably pointed downward so that the entering stream tends to lie on the wall, spreading along the wall while wetting the same, and swirling downward in a helix to enter the body of fluid at the bottom of the vessel in such swirling movement and with a minimum of turbulence and objectionable bubbles.

It will be appreciated that there is an optimum angle for the liquid to enter the vessel; this angle will be somewhere between the two extremes lying (1) parallel to the axis of the vertical vessel and (2) perpendicular to it. In the first instance, there will be no horizontal component at all to provide the swirling action which is desired, although the vertical component of the energy applied at the wall will add to the vertical component contributed by the rising bubbles in the center. In the second instance, the entering liquid will make an excessive number of revolutions around the vessel before falling to the surface of the forming pool, thus losing most of its energy uselessly to the walls of the vessel by friction. In the preferred embodiment, this angle is approximately 30° below the horizontal. For other vessel proportions the best angle may easily be found experimentally.

It must be kept in mind that there are many different kinds of bubbles which can be produced in the apparatus, and these are obviously of two types—those which are desirable, and those which are undesirable. It has been found that the larger bubbles move through the liquids quickly and may be considered of a transient nature. These are desirable, and can be used for mixing purposes since they disappear without difficulty after rising to the surface of the body of liquid in which they are formed. The undesirable bubbles are the small ones which may even be microscopic in size. These do not readily rise to the surface, do not readily break, and often will move with liquids through passageways. They cause inaccuracies when liquids containing the same are measured, they cause false counts and signals in electronic particle-detecting devices and generally can also cause contamination by adhering to vessel and conduit walls.

The invention teaches the construction of apparatus in which the formation of tiny bubbles is substantially inhibited.

Structure according to the invention provides for the mixing, retaining and transfer of liquids by suitable use of controlled gas pressure in addition to the teaching of the specific object mentioned above. Considering two vessels which are connected at their bottom ends and in which liquid will be introduced into one and thereafter transferred to the other and then drained, according to the invention gas under pressure is introduced into the second vessel before introducing the liquid into the first vessel and maintaining such pressure while running the liquid into the first vessel. As the liquid enters the first vessel and moves downward to the bottom end, it is met at the drain by gas emerging from the drain. This gas has such pressure that large bubbles displace any liquid which attempts to enter the drain of the first vessel and thereby prevent the entry of any liquid into the drain, thereby also preventing liquid from passing through the connecting conduit into the second vessel until it is desired that this occur. This time is readily controlled by the proper programming of the gas pressure apparatus. The large bubbles from the drain of the first vessel move up through the liquid retained in the first vessel and produce and up-and-down movement when combined in their effects with the downwardly swirling entry of the liquid being introduced. Even after the desired amount of liquid has been introduced, the bubbles may be continued, and since they displace liquid principally at the center of the vessel where the drain is, they continue the important up-and-down movement which thoroughly mixes the liquid. Obviously, if the liquid is already homogeneous, a minimum of time and mixing is required. Usually two liquids are introduced, not necessarily at the same time, and these must be totally intermixed. For example, in the copending apparatus it is intended that a very tiny slug of whole blood be intermixed with diluent in a very substantial volume. Unless intermixture is absolutely complete, the sample which will be used for measurement or for redilution may not be representative and the results produced by the apparatus will be false. It is obvious that absolutely not even the most minute portion of the sample can be permitted to escape during the mixing process or the sample will certainly not be representative for later use and measurement.

Additional and even more efficient intermixing may be obtained when moving liquid from one vessel into another through the bottom of the vessels, especially where the entry into the second vessel is a tangential one, so that a movement below the surface is achieved, with the entering liquid circulating through that which was first introduced and thoroughly mixing therewith. Below the surface introduction of liquid samples into other samples is substantially devoid of bubble production. All of the energy which is imparted to the liquid being introduced goes into the mixing action, with substantially none lost due to friction with container surfaces above the liquid surface.

The invention contemplates the use of vessels having a minimum of surface contact with the fluids being handled in order to minimize the likelihood of contamination from one sample to the next. Through calculus one may compute the diameter of a vessel of cylindrical configuration having a steep conical drain end which will provide the minimum of contacted surface area for a given volume of sample. If the surface area corresponding to a given vessel volume is plotted against vessel diameter, it may be seen to progress through the minimum slowly, such that appreciable changes in diameter have little effect on surface area in the region of the minimum; thus there is some latitude in the actual diameter chosen. The exact minimum value thus obtained would be optimum from a point of view of contamination of one sample by the preceeding one, but the requirement for efficient mixing by bubbles may indicate the use of a diameter somewhat smaller than this. In the apparatus which has been constructed in accordance with the invention, for a sample of 10 cc. volume, it was found that stock size tubing of 19 mm. inside diameter made up into mixing vessels gave good mixing with but a slight increase over the calculated minimum of contacted surface.

The invention also contemplates the use of gas pressure for the purpose of transferring liquid out of a vessel, either to another vessel or further on in the general apparatus with which the invention is associated. Thus, considering the structure described above in which there are two vessels, comprising a first vessel which has liquid being introduced in it, and a second vessel which is connected to the first by way of a conduit connected to the drain of the first vessel and entering the second vessel at a tangent, it has been devised that gas pressure keeps the entering liquid from going into the connecting conduit while at the same time furnishing bubbles for mixing the liquid in the first vessel. There is an outlet port in the upper part of the first vessel to permit escape of gas, an an inlet port in the upper part of the second vessel by means of which to introduce the gas. These ports conveniently can be connected to a gas control apparatus and can serve in several capacities.

When the intermixture has been completed and it is desired to transfer the liquid from the first vessel into the second, the ports are interchanged by the gas control apparatus. The port of the first vessel is connected to a source of gas pressure and the port of the second vessel is connected to exhaust. Under these conditions the gas will now blow the liquid from the first vessel into the second in the manner described above with the continually reduced pressure until complete drainage has been achieved. This may be referred to as a tapered application of pressure.

Various modified structures are contemplated by the invention. The methods described comprise an important aspect of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic or block diagram showing a portion of an automatic fluid-handling system which includes structures of the invention.

FIG. 2 is a side elevational view of a piece of glassware formed of two separate vessels and constructed in accordance with the invention, a portion being broken away and shown in section.

FIG. 3 is a sectional view taken generally along the line 3–3 of FIG. 2 and in the indicated direction.

FIG. 4 is a sectional view taken generally along the line 4–4 of FIG. 2 and in the indicated direction.

FIG. 5 is a schematic diagram illustrating another form of apparatus constructed in accordance with the invention.

FIG. 6 is a schematic diagram illustrating a plurality of systems which may be operated in different manners, depending upon the presence or absence of certain connections and valves, the view being more for explanatory purposes than for illustrating any particular form of structure.

FIG. 7 is a schematic diagram illustrating a system using a single vessel in accordance with the invention, such illustration being used also to describe a method of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In FIG. 1 there is illustrated a system for the handling of liquids, this being a simplified form of the structure disclosed, for example, in the copending application. As stated, the purpose of such structure is to process whole blood or the like fluid to ascertain certain parameters thereof by measurements and computation.

In the diagram, the vessels which are provided in accordance with the invention are those which are designated **10, 12, 14, 16** and **84**, other structure taught by the invention being connected therewith. The vessels are mixing chambers, and while they are intended to operate primarily in pairs as vessels **10, 12** and vessels **14, 16** in this diagram, single vessels, such as **84**, may be used under many conditions.

The blocks **18, 20** and **22** at the top of the view comprise liquid sources A, B and C, respectively. The sources may be, for example, in the apparatus described, blood, diluent, and so on. The large block **24** is designated mixing valve means, and this comprises an arrangement of metering valves for controlling the introduction of liquids into the system, such block being considered also to include substantial apparatus such as pumps, conduits and the like. The block **26** at the left which is designated program and control means represents an overall control for the entire system.

Consider, for example, that measurements are to be made of blood indices such as white and red blood cell counts. The mixing valve means **24** draws in a sample from the liquid source A at **18** by way of a line **28** and introduces a precise quantity of the sample along with a precise quantity of diluent into the first vessel **14** by way of a line **30**. The diluent may be obtained from the liquid source **20** by way of the line **32**.

According to the invention, gas, such as, for example, air under pressure, is applied to the inlet port **34** of the line **36** to the interior of the vessel **16** at the top thereof. This gas fills the vessel **16** and passes out the bottom end thereof. The control of the gas is achieved through suitable gas valve means **40** which receives its supply from a line **42** and is programmed by way of a line **64** from the program and control means **26**.

It will be recalled that one of the features of the invention consists of the use of gas for the purpose of controlling the entry of fluid into a vessel and in this instance, entry of the liquid by way of the line **38** into the vessel **16** is controlled by the introduction of gas into the vessel **16** at the port **34**. At the time that the liquid starts to flow, gas is emerging at the bottom of the vessel **14** by way of the line **38**, and is leaving by way of a port **44** and a line **46**. The liquid introduced by the mixing valve means **24** remains in the vessel **14** and is thoroughly mixed by the large bubbles which rise from the line **38**. The bubbles produced by gas coming from the vessel **16** are large. Preferably, the apparatus is adjusted so that these bubbles are visible, say on the order of 1,000 to 3,000 microns in diameter, rising very fast and disappearing quickly. Minute bubbles substantially smaller than that dimension, besides remaining in suspension long enough to be counted later as particles, would adhere to the walls of the vessels and conduits.

After a given time controlled by the program and control means **26**, the liquid from the vessel **14** is permitted to pass through the line **38** into the vessel **16** where additional mixing occurs. The gas valve means **40** converts the ports **34** and **44** from inlet and outlet respectively to outlet and inlet, so that pressure is being applied in the vessel **14** above the liquid body therein, forcing the same through the line **38** into the vessel **16**. As previously mentioned, in transferring the liquid from the vessel **14** to the vessel **16**, the pressure is reduced in a tapered manner, that is, as the volume of liquid in the vessel **14** decreases, the pressure decreases so that there is no violent stream of bubbles shot into the body of liquid in the vessel **16** at the end of the transfer, and yet all of the liquid is so transferred. If desired, after the liquid has been transferred, some gas may continue to be pumped slowly into the vessel **16** in order to produce the additional intermixing, although introduction of the liquid at the bottom of the vessel **16** does provide mixing while transfer is occurring.

After it is certain that the liquid in the vessel **16** has been thoroughly mixed, a portion of the liquid is removed by a siphon or thief **48** that dips down into the vessel **16**.

It will be understood that the first dilution was made for the purpose of producing a dilution of blood cells which may be eventually limited to white blood cells, and the liquid in the vessel **16** is intended for this purpose. Since the red blood cell count must be made at a much higher dilution, for the same sample, a dilution is made of the first dilution and this is the reason for withdrawing a small portion by way of the thief **48**. It will be seen that the thief **48** is connected to the mixing valve means **24** by way of a line **50** and the liquid from this line is transferred from the mixing valve means by way of a line **52** into the vessel **10** shown on the left, this being the first vessel of the pair interconnected by the conduit **54**. The mixing valve means **24** dilutes the liquid in the line **50** which passes through it by means of diluent obtained from another source **22** which is the source C by way of the line **58**, so that the vessel **10** receives the concentrate and diluent in quick succession. Proper metering assures that the dilution obtained in the vessel **10** is the correct one for the measurements to be made and this depends not only upon the metering mechanism of the valve means **24** but also requires that the thief **48** withdraw an absolutely representative sample from the vessel **16**. Again, this in turn depends upon perfect mixing.

In the vessels 10 and 12, the same process of intermixing and transfer occurs as described in connection with the vessels 14 and 16. Gas valve means 60 also controlled by the program and control means by way of a control channel 62 serve the same function as the gas valve means 40. The ports 66 and 68 and the lines 70 and 72 respectively are the equivalents of the ports 44 and 34 and the lines 36 and 46 and operate in the same manner.

In the case of the liquid from the chambers 10 and 12, the discharge occurs through the outlet drain 73 and the valve 74, this latter valve being under the control of the program and control means 26 by way of a control channel 76. This is the red blood cell dilution and it is passed to a suitable counting device, such as a Coulter apparatus designated as measuring apparatus R in the block 77. As for the liquid in the vessel 16, since this liquid is to be used for the white cell determination, it is first passed out of the drain 78 through the valve 79, this valve being controlled by the control channel 80. The liquid passes into the line 82 and thence into the lysing vessel 84. This vessel may be of the same construction as those previously described, with tangential entry and the presence of gas under pressure for mixing, holding and transfer. Additionally, there is a second fluid introduced into the vessel 84 by way of line 86 from a fluid pump 88, this pump serving to bring liquid from a fourth liquid source 90 under the control of the control channel 92 also operated by the program and control means 26. The liquid which is introduced in the line 86 is a lysing agent. After lysing, the resulting fluid may be run out through the valve 94 to the line 95 which carries the same into a measuring apparatus W at 96, this preferably being a Coulter apparatus also. The valve 94 is operated by means of the control channel 97 from the program and control means 26.

It will be seen that there is a gas source 43 which serves as a supply for the entire apparatus, such source being connected to the several gas valve means 40, 60 and 89 by the lines 42. Also, each gas valve means has an exhaust, the purpose of which is understood. The vessel 84 has a line 99 by means of which the gas may be introduced from the gas valve means 89 or exhausted from the vessel 84.

In transferring fluids attention might be drawn to the use of a line which passes out of a vessel and into another at a higher level so that a pressure head is required to be overcome to pass the fluid, This is easily accomplished by the use of the gas under pressure as described and, additionally, the line is blown free of the liquid. No valves are needed in such case, and by suitable control of the gas, very accurate control of the liquid movement is achieved. Other portions of the apparatus do require valves of different kinds and most of them are of an automatic variety readily available commercially.

In FIGS. 2, 3 and 4 the details of the structure of a dual vessel-mixing device are shown. This comprises the structure including the vessels 14 and 16. The vessels are shown capped at 100 and 102 so that they may be used in the manner contemplated, although it will be understood that the basic concept of tangential entry of fluids may be used with open vessels. The line 30 (FIG. 1) is connected to the fitting 104 which is shaped to join with the wall of the vessel 14 so that its bore 106 enters the interior of the vessel tangential to the inner surface as best shown in FIG. 3. Also, the angle of the bore 106 is such that the entering stream of liquid will be pointed slightly downward, as best shown in FIG. 2. When liquid enters the vessel, it will spread smoothly on the interior surface of the wall of the vessel, wetting the wall, and will swirl downwardly in a helix as indicated by the broken line 108 of FIG. 2. It will form a swirling pool at the bottom with a minimum of turbulence and hence a minimum of minute bubbles.

As previously explained, in the meantime gas under pressure is forced into the chamber 16 by way of the port 34, enters the bore 110 of the conduit 38 and emerges at the drain hole 112. It prevents the liquid gathering in the bottom of the vessel from entering the bore 110 so long as the pressure is applied, and large gas bubbles rise up from the drain hole 112 through the liquid (see, for example, FIG. 5) thereby mixing the liquid in an up-and-down movement. It then passes into the space above the liquid in the vessel 14 and out through the port 44.

When the liquid is transferred from one vessel to another, the ports 34 and 44 change their functions. Pressure is applied through the port 44 and gas permitted to escape through the port 34. The liquid is forced through the bore 110 and it enters the bottom end of the vessel 16 also on a tangent at 114 (FIG. 4) so that there will be a minimum of turbulence in transfer. Since the valve 79 (FIG. 1) will normally be closed at this time, the liquid will accumulate in the bottom of the vessel 16, and the entering liquid at 114 will create a swirling pool which will thoroughly mix the liquid. Due to the small diameter of the path 78, the liquid will be excluded from it by the entrapped gas above the valve 79. As explained, the liquid introduced into the vessel 14 may comprise a slug of highly concentrated liquid and diluent, and where a thorough mixing is to be assured, the use of two vessels is indicated. Under many circumstances, one of the vessels may be eliminated.

It will be seen that the first vessel 14 has the entry of the liquid substantially above the level of the liquid. This assures a minimum of contamination since nothing but the diluent which follows the sample plug can come in contact with the inlet port. This is done even though better mixing may be obtained when the liquids are introduced below the surface and even though such lower introduction enables vigorous mixing without the danger of generating undesirable bubbles of very small size, because of the paramount importance of freedom from contamination.

As previously mentioned, the diameter of the tubing from which the vessels 14 and 16 is formed would be chosen on the basis of the volume of liquid handled so that there will be an optimum tradeoff between a minimum of surface engaged by the liquid and maximum efficiency of mixing by bubbles.

Reference may be had to the thief 48, which it will be seen, has its lower entrance slightly below the level of the entrance 114. This is done in an effort to prevent the possibility of bubbles being drawn into the line 50.

FIG. 5 illustrates generally a single mixing vessel 120 which has an inlet fitting 122 quite similar to the fitting 104 in FIG. 2, so that liquid may be introduced into the vessel 120 tangentially, generally, along the broken line 121 which is in the form of a helix. There is a gas port 124 at the top of vessel 120 entering through the cap 123 and gas from a source 125 controlled by the gas control means 126 may be introduced or exhausted by way of a line 127. The gas may also be introduced in the drain 128 by way of a line 130, also controlled by the gas control means. As previously discussed, the introduction of gas into the drain 128 produces large bubbles which rise through the body of liquid, and while preventing the liquid from entering the drain 128, also serves to mix thoroughly the liquid by an up-and-down movement represented by the small broken arrows 132. Gas is exhausted from the gas control means 126 by way of the exhaust line 134. The outlet valve 146 enables transfer of liquid through drain 128, being programmed in any suitable manner as indicated by control channel 147.

The diagrammatic structure illustrated in FIG. 6 includes connections and fittings which render the structure suitable for a wide variety of applications. Thus, considering only the equivalent structure shown in FIGS. 2, 3 and 4, the same is identified in FIG. 6 by the prefix 6 using the same characters of reference. Mirror structure is provided for versatility, identified by the prefix 6 and the prime added to the same characters of reference. In addition to the structure mentioned, there are shown inlet ports at 601 and 601' for enabling the introduction of liquid from external sources into the interior of the respective vessels, and a plurality of valves. These valves are designated V1, V2, V3, V4 and V5 and their control may be obtained from programming and control means which are not illustrated. For the most part gas pressure is used to assure proper transportation. It may be assumed that the same constructional details are used in forming this device, and that some of the parts may be omitted or further duplicated. Entrance ports such as 604 and 604' are tangential; the dimensions of the vessels are such that the minimum wall surface consistent with good mixing is contacted by the volume of fluid to be handled; port entrances at the bottom of the vessels are tangential to promote swirling movement upon entry of liquids; and the size of conduits such as those draining and communicating between vessels is optimum. This has not specifically been mentioned above, but it was pointed out that capillarity due to very small diameter conduits must be avoided. On the other hand, the size must be small enough so that gas may be used to control the fluid, as, for example, to enable it to be held in a vessel without draining by the expedient of introducing gas into the drain. This dimension for the structure of said copending application handling blood dilutions has been chosen at approximately one-sixteenth inch in diameter.

In FIG. 6, many different schemes of operation can be utilized. For example, with the valves V1, V2, V3 and V4 closed, gas being introduced at 636 and the valve V5 connecting only the line 6114 with the line 638, liquids may be introduced at 604 and/or 601. Bubbles will enter drain 6112 and mix the liquid in the vessel 614 and escape through the port 646, which here acts as an exhaust. No liquids are introduced at 604' or 601'. If desired, the valve V5 may be arranged to enable the gas during this period of time to pass by way of the drain 6112' and the line 638' into the vessel 614.

After the liquid has been sufficiently mixed, the gas ports 636 and 646 are changed, so that gas is introduced at 646 and exhausted at 636. The liquid from the vessel 614 passes into the vessel 616 along any chosen path, depending upon the construction and operation of the valve V5. After entering this vessel, additional liquids may be introduced at 604' and 601' and additional mixing may take place, not only during entry of the liquids, but even afterwards, by permitting the gas to continue to bubble through the liquid, either from the entrance line 6114 or by way of the line 638'. Thereafter, by suitable valve manipulation and gas control, the liquid may be discharged through the drain 678 and the valve V3.

During this period, it is feasible to introduce additional gas at 678 through the valve V1 for mixing or the like.

Other possible arrangements and programming will be obvious from a study of the apparatus illustrated in FIG. 6.

FIG. 7 illustrates a novel valve system which utilizes the invention, illustrating especially the manner in which a tapered gas pressure may be achieved for drainage purposes, as explained above.

The vessel 160 may be considered the equivalent of a vessel such as illustrated in FIG. 5, for example, and it is provided with a gas port 162, a liquid inlet port 164 near the top of the vessel, a drain 166 which is the equivalent of the drain 128, a lower gas inlet port 168 and valve 169, and outlet valve 170 which is the equivalent of the valve 146. The construction of the elements thus far mentioned is as previously described.

The block 172 is a source of gas which is connected by the line 174 with a pressure regulator 176 that controls the pressure of gas which is run into a storage tank 178 that is called pressure vessel in the view. The pressure regular is connected to the pressure vessel 178 through a two-way valve 180 by the interconnecting lines 182 and 184. The program and control means 186 has control channels to various parts of the apparatus, as indicated at 188, 190, 192 and 194. The pressure vessel 178 connects by the line 196 to a manually adjustable needle valve 198 which in turn operates through a line 200 which passes the gas to a three-way valve 202.

This three-way valve 202 is connected to line 206 in such a manner as to enable the gas inlet port 162 in vessel 160 to be connected by way of line 206 with the exhaust line 204 or the gas pressure inlet line 200.

The pressure regular 176 also controls the gas pressure through a manual needle valve 210 by way of line 208. The gas passing through needle valve 210 is passed to valve 169 by line 212.

When liquid is entering the vessel 160 through the inlet 164, the valve 170 is closed, this condition being achieved by the control channel 194 which may be operated by the control means 186 or some other control means in a different part of the system. The valve 169 is open under control of the program and control means 186 by way of the channel 190 so that it is connected by the line 212 with the manual needle valve 210 which is receiving gas under pressure from the source of gas 172 either through the pressure regulator 176 or some other regulator by way of line 208. Also the three-way valve 202 is ported in the manner allowing port 162 in vessel 160 to be connected to exhaust 204 through line 206. Thus, gas will be bubbling through the drain 166 into the body of liquid, serving to mix the same while preventing any of the liquid from moving down into the drain. This gas will leave the system through exhaust 204, along with the gas in vessel 160 displaced by the entering liquid.

It is desirable to maintain valves 169, 170, and 202 in this mode of operation until all the prescribed liquid enters and until the swirling of the liquid body subsides, to achieve the highest quality of mixing.

When the liquid has been thoroughly mixed, the valves 169, 170, and 202 are operated to their second states to achieve emptying, by signals from the program and control means 186 through control channels 190, 194 and 188. Means are provided to prevent the escape of gas from the fluid inlet 164 by such expedients as a positive displacement pump at 88 or mixing valve means at 24 of FIG. 1.

The condition of the system in this state is as follows: Valve 169 is shut off preventing further flow of gas out of drain 166. Valve 170 is opened allowing liquid to pass out of drain 166 through tube 171 to the next stage of sample processing, not illustrated in FIG. 7. Three-way valve 202 is ported in the manner allowing gas flowing through needle valve 198 to pass into vessel 160 by way of lines 200 and 206 through port 162. In addition, two-way valve 180 is opened by means of control channel 192 from program and control center 186. Thus, the pressure vessel 178 is filled with gas at a pressure that is controlled by the regular characteristics. This could be some value such as, for example, 5 pounds per square inch, easily maintained.

Due to this pressure in vessel 178 needle valve 198 allows a gas flow into vessel 160 at port 162 through the three-way valve 202. This gas entering vessel 160 creates a gas pressure above the fluid level in vessel 160 which is adjustable by needle valve 198 to the magnitude required to force the liquid in the vessel 160 out of the drain 166 and along tube 171 at the desired rate of speed.

This portion of the liquid transfer operation will maintain a constant liquid transfer rate out of drain 166 and tube 171 because of the following conditions: when tube 171 is full of liquid moving at a given velocity, the friction between the liquid and the wall of the tube 171 will be a given value and the pressure drop across needle valve 198 will stabilize at a substantial value. The force applied by the gas in vessel 160 onto the surface of the liquid therein is the only force applied to the system other then gravity. If the frictional forces encountered in tube 171, which is acting against the remaining gas pressure force in vessel 160, is equal to the gas pressure force and the force of gravity, there will occur no net gain or loss in the flow velocity. So if there is a constant liquid flow velocity through tube 171 there must be a constant gas pressure force in vessel 160 above the remaining liquid. This implies that there must be a constant gas pressure acting upon the liquid to achieve the condition of constant flow. Since the gas occupied volume of vessel 160 is increasing as the liquid leaves drain 166, a uniform flow rate of gas into port 162 is necessary to maintain the gas pressure at a constant level in vessel 160. The constant flow is accomplished by the pressure regulator 176 and the needle valve 198 which are at this time connected to vessel 160 by lines 206, 200, 196, 184 and 182 and components 202, 178 and 180.

This constant rate of liquid transfer is maintained by the control center **186** until vessel **160** is almost empty at which time control center **186** signals valve **180** to change state by way of control line **192**. This will cause the previously mentioned tapered decrease in emptying velocity from vessel **160** through tube **171** so that the velocity of the existing liquid will be practically zero by the time the last drop of liquid emerges from tube **171**.

Normally, as in the preferred embodiment of the invention, the frictional forces in the liquid-bearing lines **166** and **171** and in the needle valve **198** will be large with respect to the inertial forces due to the mass and velocity of the various fluids. When this is the case, the pressure used to accomplish this will also be substantially zero. If the mass and/or velocity of the fluid is so large that inertia is not negligible, however, the capacities of gas occupied volumes may be so adjusted that a negative or braking force is applied to the liquid surface at this time.

Braking action is accomplished in the following manner: At the proper moment two-way valve **180** is shut off by means of control line **192** from control center **186**. As gas from pressure vessel **178** escapes through needle valve **198** the pressure in vessel **178** begins to decrease. As this pressure decreases, the flow rate of gas through the needle valve decreases and hence the flow rate of gas into vessel **160** decreases. When this happens the pressure in vessel **160** decreases which causes a decrease in the force on the remaining liquid in vessel **160** and hence a decrease in the flow rate of liquid out of tube **171**. This continues until there exists no more pressure in vessel **178**. The adjustment of the system is accomplished by the adjustment of needle valve **198**, which effects this stage of emptying along with the previous stage of constant flow emptying of vessel **160**, so that for a set of given conditions of program and control time and pressure vessel **178** size a satisfactory condition of emptying may be found.

It should be apparent that considerable variations of the apparatus and method of the invention are capable of being made without in any way departing from the spirit or scope of the invention as defined in the appended claims.

I claim:

1. Structure for automatically handling liquids in mixing and transfer apparatus, which comprises

A. at least one vessel having an entrance port for liquid, the said entrance port being spaced substantially above the level of the liquid after said liquid has fully entered and been retained in the vessel,

B. said entrance port being arranged to direct an entering stream of liquid in such a manner against the inner surface of the vessel so as to cause most of the liquid to flow along said surface before collecting at the bottom of the vessel and to impart a horizontal component of rotary motion to said liquid,

C. means for imparting a vertical component of mixing motion to said liquid in said vessel,

D. and means for draining said liquid from said vessel after mixing, including an outlet at the bottom of said vessel.

2. Structure as claimed in claim **1** in which said means for imparting a vertical component of mixing motion prevents draining of liquid during operation thereof.

3. Structure as claimed in claim **2** in which said vertical component-imparting means comprise a source of gas of a pressure higher than that of the gas above the liquid of said vessel connected to said vessel at least at said outlet for introducing bubbles at the bottom of said vessel into the liquid in said vessel.

4. Structure as claimed in claim **3** in which said vessel is enclosed but for said liquid entrance port and outlet, and said draining means include, in addition, a gas source and a gas inlet above the liquid of said vessel whereby to enable introduction of gas under pressure to expel the liquid of said vessel out of said outlet, and in which control means are provided to discontinue introduction of gas at the top of the vessel when it is being introduced at the bottom, and vice versa.

5. Structure as claimed in claim **4** in which said sources are combined in one, said control means include gas flow switches, and in which said gas inlet above the liquid is arranged to exhaust gas when said bubbles are being introduced.

6. Structure as claimed in claim **1** in which said draining means include, in addition, means for establishing a gas pressure differential above and below the liquid of such degree as to cause the liquid to be expelled from said outlet.

7. Structure as claimed in claim **6** in which said last means are provided with a pressure control device to taper the pressure differential while the liquid is being expelled.

8. Apparatus as claimed in claim **1** in which the means for imparting a horizontal component of mixing motion include arranging the entrance port so that the stream of entering liquid has a component tangential to the essentially circular transverse cross section of the vessel.

9. Apparatus as claimed in claim **1** in which the means for imparting vertical and horizontal components are so proportioned as to produce a maximum of swirling action for mixing purposes.

10. Apparatus as claimed in claim **1** in which the vessel is substantially circular on its interior and the diameter of the inner surface is chosen with respect to the volume of liquid which is to be handled by the apparatus so that the surface contacted by the liquid when the entire volume has entered and been retained in the vessel is substantially minimized.

11. Structure as claimed in claim **1** in which said vertical component imparting means include a gas source and means for establishing a first pressure differential of said gas above and below the liquid in the vessel so that during entering of the liquid bubbles will pass from the outlet up through the liquid, in which said means also are adapted to establish a second pressure differential of said gas above and below the liquid in said vessel so that the liquid may be expelled through said outlet on account of said second pressure differential, and there being control means for establishing said pressure differentials mutually exclusive of one another whereby to have bubble mixing without draining during entry of the liquid, and thereafter draining without bubble mixing.

12. Structure as claimed in claim **11** in which said control means tapers the second pressure differential while the liquid is draining.

13. Apparatus as claimed in claim **1** in which the means for imparting a vertical component of mixing motion include arranging the entrance port so that the stream of entering liquid is slanted downward.

14. Structure for automatically handling liquids in mixing and transfer apparatus, which comprises:

A. a pair of vessels connected one to the other for functioning together as a mixing device,

B. the first vessel having a first liquid entrance port spaced substantially above the maximum level of the liquid which is adapted to be collected in said first vessel, a first gas port at the top of said first vessel, and a first drain outlet at the bottom of the first vessel,

C. the second vessel having a second liquid entrance port adjacent its bottom end but substantially below the normal level of liquid in said second vessel, a second gas port at the top of the second vessel, and a second drain outlet at the bottom of the second vessel substantially below the second liquid entrance port,

D. a conduit providing the said connection between vessels and extending from the first drain outlet to the second liquid entrance port,

E. the said first entrance port being arranged to direct an entering stream of liquid in such a manner against the inner surface of the said first vessel so as to cause most of the liquid to flow along the said inner surface before collecting at the bottom of the vessel and to impart a horizontal component of rotary motion to said liquid,

the liquid adapted to be collected in the first vessel and mixed while being so collected, then transferred to the second vessel by way of said first drain outlet, conduit and second liquid entrance port and being mixed while collected in said second vessel, and thereafter expelled from said second vessel by way of said second drain outlet.

15. The structure as claimed in claim 14 in which said first liquid entrance port includes a fitting arranged with a bore for the liquid substantially tangential with the interior surface of said first vessel and slanted generally downward.

16. The structure as claimed in claim 15 in which the second liquid entrance port is arranged to direct an entering stream of liquid in a generally tangential direction relative to the bottom of the second vessel so as to produce swirling in the liquid being collected in the second vessel below the level of said liquid.

17. The structure as claimed in claim 14 in which there is a gas source connected with said gas ports and control means to establish a pressure differential between vessels through said conduit so that when said stream of liquid is entering said first vessel, gas bubbles emerge from said first drain outlet preventing entry of liquid therein while at the same time bubbling up through the liquid in said first vessel to impart an up-and-down mixing to said liquid.

18. The structure as claimed in claim 17 in which said control means constitutes said first gas port an exhaust port and said second gas port an inlet port while said stream of liquid is so entering said first vessel.

19. The structure as claimed in claim 17 in which said control means is arranged to change the said pressure differential after the liquid in said first vessel is mixed whereby to cause the liquid from the first vessel to be expelled into said first drain outlet, through said conduit, and by way of second liquid entrance port into said second vessel, means being provided to block the second drain outlet of said second vessel until it is desired to drain the liquid therefrom.

20. The structure of claim 19 in which said control means include structure for tapering the pressure differential during the expelling of liquid so that the pressure of the liquid stream entering the second vessel decreases as the expelling proceeds.

21. The structure as claimed in claim 17 in which said control means constitutes said first gas port an exhaust port and second gas port an inlet port while said stream of liquid is entering said first vessel, and vice versa when said liquid is entering said second vessel.

22. The structure of claim 21 in which said control means include structure for tapering the pressure differential during the expelling of liquid so that the pressure of the liquid stream entering the second vessel decreases as the expelling proceeds.

23. The structure as claimed in claim 14 in which the second liquid entrance port is arranged to direct an entering stream of liquid in a generally tangential direction relative to the bottom of the second vessel so as to produce swirling in the liquid being collected in the second vessel below the level of said liquid.

24. The structure of claim 14 in which means are provided to siphon liquid from said second vessel, said siphon means opening to said second vessel above the second drain outlet but below the second liquid entrance port.

25. A method of mixing liquid entering a vessel at the top thereof and adapted to be drained from a drain at the bottom thereof, which comprises: directing the entering stream of liquid into said vessel on substantially a tangential path against the interior wall thereof so that the liquid is thereby given a primarily horizontal rotative component while it collects at the bottom of the vessel and a vertical component due primarily to gravity, and in which relatively fast-moving gas bubbles are introduced at the bottom of the vessel at the center thereof to provide an additional vertical mixing component.

26. A method of mixing liquid entering a vessel at the top thereof and adapted to be drained from a drain at the bottom thereof, which comprises: directing the entering stream of liquid into said vessel on substantially a tangential path against the interior wall thereof so that the liquid is thereby given a primarily horizontal rotative component while it collects at the bottom of the vessel and a vertical component due primarily to gravity, and in which relatively fast-moving gas bubbles are introduced in the center of said vessel at the bottom thereof while the stream of liquid is entering whereby to prevent the liquid from draining from the vessel and providing an additional vertical mixing component to said liquid.

27. The method of claim 26 in which said bubbles are continued to be introduced after the liquid has entered but before it is drained.

28. The method of claim 26 in which, after the liquid has been mixed, the bubbles are discontinued and pressure applied above the liquid to expel the same from the vessel through said drain.

29. The method of claim 28 in which said pressure is decreased as the liquid drains.

30. A method of mixing liquid entering a mixing device comprising a pair of bottom-connected static vessels which comprises: introducing the liquid into the first vessel in a swirling movement while applying a first pressure differential between vessels effective through their bottom connection to prevent drainage of liquid from the first vessel into the second, collecting and mixing the liquid in the first vessel while maintaining said pressure differential, applying a second pressure differential to expel the liquid from the first vessel to the second with a swirling movement in the second vessel and collecting the liquid in the second vessel, and draining the liquid from the second vessel after it has been collected and mixed in said second vessel.

31. The method of claim 30 in which said first pressure differential produces bubbles which pass from the second vessel through the connection into the bottom of the first vessel and bubble through the liquid collecting in the first vessel.

32. A mixing device for use in a blood-diluting apparatus which comprises, a pair of vertically arranged vessels each forming a separate chamber, and having a conduit connecting them at their bottom ends, one chamber being shorter than the other whereby the connecting conduit is at an angle, an entering pipe integral with the shorter tube and having a bore disposed to direct the entering stream at an angle downward and tangential to the inner surface of the wall of the shorter chamber, the larger chamber having a drain at its bottom end.

33. The mixing device of claim 32 in which means are provided for connecting an air stream with both chambers at the top thereof in a selected manner for assisting in mixing, transferring and draining.

34. A mixing apparatus for liquids comprising, a vessel having an upper entrance port and a lower drain port, a first gas port at the top of the vessel and a second gas port in the bottom of the vessel, a source of gas under pressure, a gas pressure accumulator and means for establishing a predetermined pressure in the accumulator from the source, a gas control system connected with said accumulator and source and having connections with the vessel to introduce gas at the second port and exhaust it from the first port while liquid is being introduced into the vessel at the top thereof and accumulated in the bottom, said gas control system having switching means for discontinuing the introduction of gas into the second port and connecting the accumulator to the first port, whereby to expel the liquid from the vessel under pressure.

35. The structure of claim 34 in which the switching means disconnects the source from the accumulator when connecting said accumulator to said first gas port whereby the pressure of gas above the liquid from said accumulator will decrease while the liquid is being expelled from said vessel.