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[54] **SYSTEM FOR PROCESSING AND ANALYZING BIOLOGICAL SAMPLES**
4 Claims, 2 Drawing Figs.

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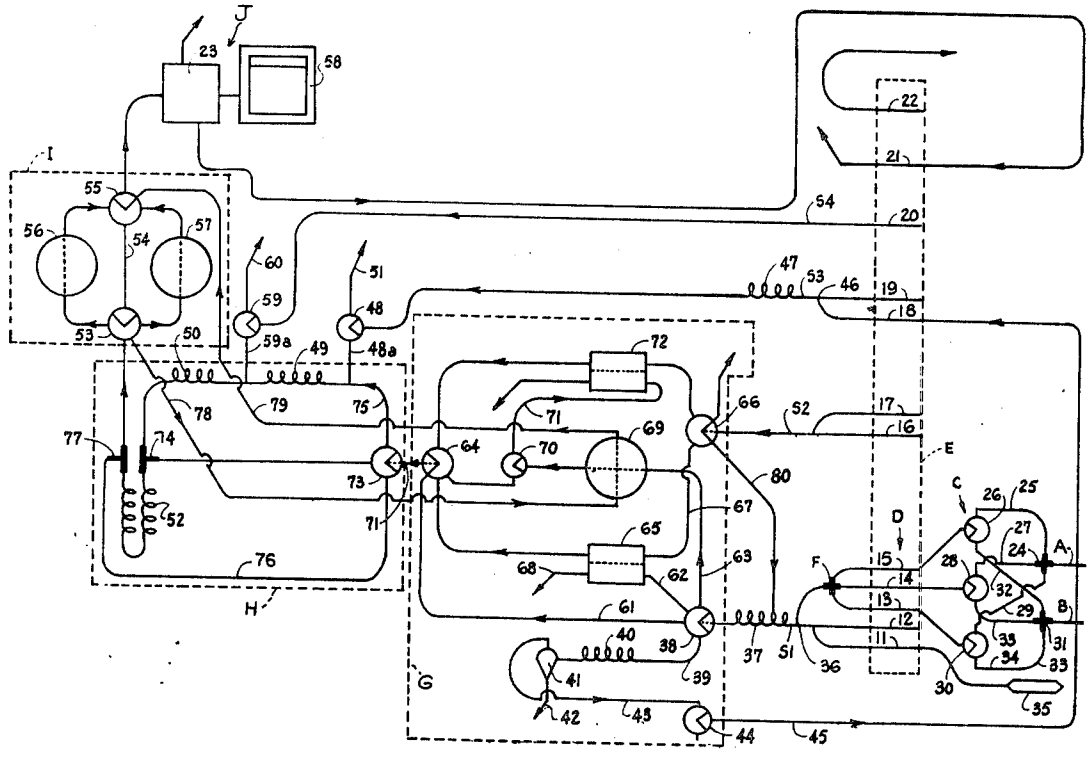
ABSTRACT: A system for analyzing biological samples which includes a valving arrangement that cooperates with various size tubing so that a sample can be mixed with a diluent to a desired degree of concentration. The system is adapted to be programmed so that reagents and the like can be added to the sample according to the test being run.



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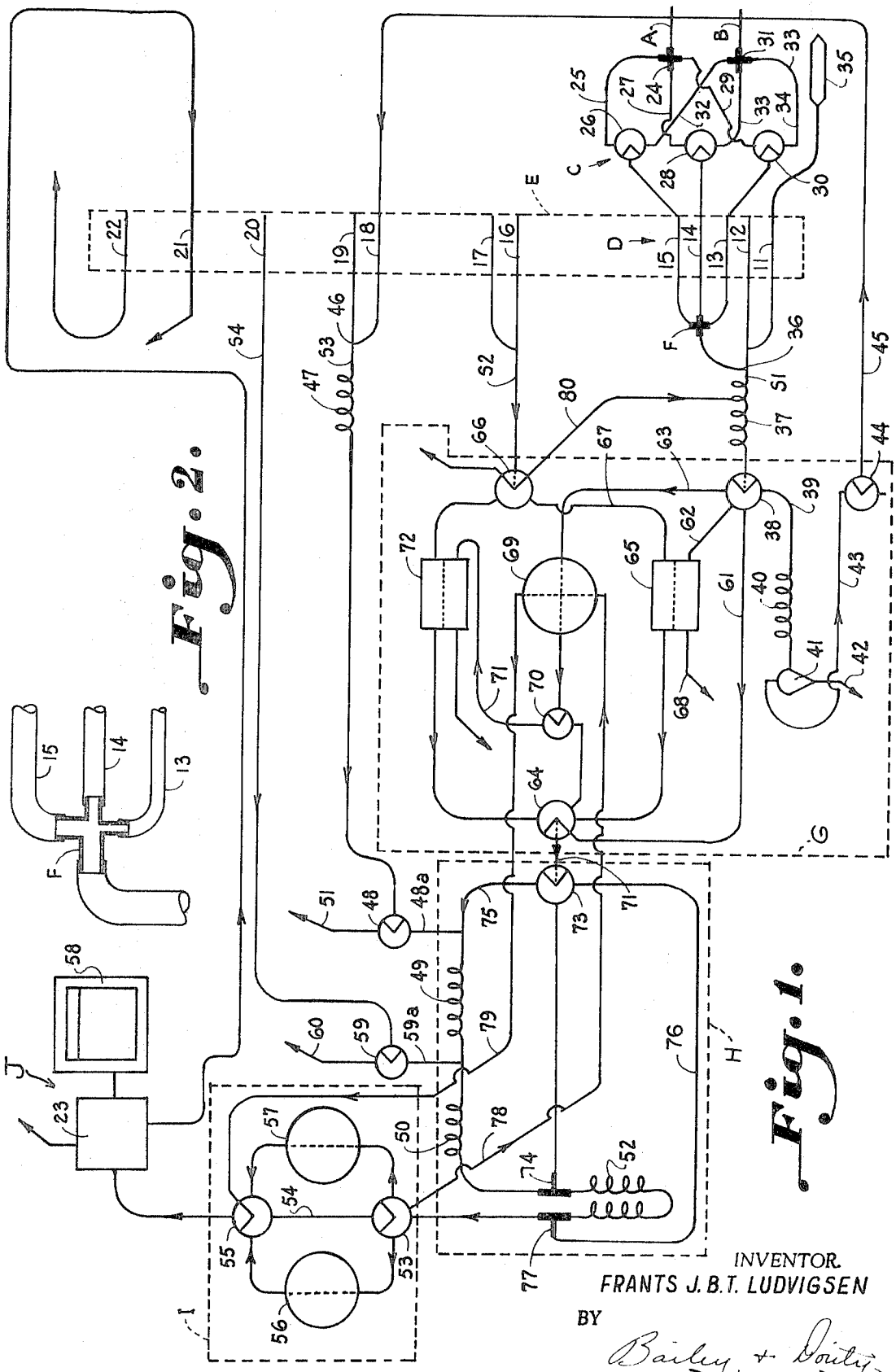

Fig. 2.

Fig. 1.

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SYSTEM FOR PROCESSING AND ANALYZING BIOLOGICAL SAMPLES

This invention relates to a testing manifold which is provided for automatically performing clinical analysis of biological samples.

For many years automatically operated analyzers for analyzing biological samples have been very successful and heavily used in clinical and other analytical laboratories. Examples of such automatically operated analyzers are illustrated in U.S. Pat. No. 3,098,717 granted to Ferrari, Jr., on July 23, 1963, and U.S. Pat. No. 3,047,367 granted to Kessler on July 31, 1962. The automatic analyzer principle includes generating a series of air-segmented streams on a proportional pump operated on a peristaltic principle. These streams are combined and recombined after passage through a series of processing modules, such as mixing coils, heating baths, dialyzers, etc., and are finally sent to a colorimeter which automatically analyzes the sample and records the result on a permanent recorder.

Although this system has been of a tremendous value to the clinical chemist, both from the point of view of familiarity with operation and easy access for repair, and also for instructional purposes, there are, however, certain drawbacks to this technique. For example, for each different analysis of a particular sample the tubing had to be changed and interconnections of the various modules had to be made according to the chemical principle of the particular analysis. The changing of the tubing enhanced the possibility of making errors in running tests and also occasionally resulted in breaking of glass connections, losing or loosening of nipples, transmission tubing popping off because of aging of the end, etc. Not only is there a chance of an error in making the tube connections, such an operation is time consuming occupying a considerable amount of the operator's time.

Accordingly, it is an important object of the present invention to provide an analyzer which is readily adaptable to perform a plurality of various tests on biological samples.

Another important object of the present invention is to provide an analyzer which incorporates a system for combining a stream of test sample with a stream of diluent so that a constant volume stream of sample of a predetermined concentration can be produced for subsequent analysis.

Another important object of the present invention is to provide an analyzer which is relatively simple to operate and can be programmed to perform various tests by merely changing valve settings.

The construction designed to carry out the invention will be hereinafter described, together with other features thereof.

The invention will be more readily understood from a reading of the following specification, and by reference to the accompanying drawing forming a part thereof, wherein an example of the invention is shown and wherein:

FIG. 1 is a schematic diagram of the analyzer illustrating in particular the flow chart through the various treatment stations thereof, and

FIG. 2 is an enlarged fragmentary view, partially in section, illustrating tubing for combining a diluent with a stream of test sample.

The drawing illustrates an automatically operable analyzer in combination with a system for concomitantly consolidating a stream of diluent with a stream of test samples so that a constant volume stream of sample of a predetermined concentration can be produced for analysis by the analyzer. The system includes a sample tube A which carries a stream of sample from a suitable reservoir (not shown) such as a test tube or the like. A first junction means is provided for receiving the stream of sample. A diluent tube B carries a stream of diluent from a suitable reservoir (not shown) and feeds such to a second junction means. At least three control valves C, each having at least a pair of inlets and an exit, are provided for receiving the stream from the first and second junction means. Both first and second junction means are coupled to a respective inlet of each of said valves. The valves can be set for providing communication from a particular inlet to an exit.

Three tubes D of varying internal diameters are connected to respective exits of the control valves and are stretched across a proportional pump E. The proportional pump E causes a continuous stream to flow through the three tubes D. A third junction means F is coupled to the other end of the three tubes D for receiving the streams flowing therethrough and combining said streams into a single stream of a constant volume of sample of a predetermined concentration. The continuous stream then passes through a plurality of treatment circuits G through J, respectively, wherein the stream is processed so that a particular test can be performed thereon.

A total of four streams, S1 through S4 are generated on the manifold by tubes 11 through 20. In addition, tube 21 is a return from a flow cell 23 which is part of the colorimeter J. Water is pumped through tube 22 by the proportional pump E to any suitable water reservoir.

The free end of the sample tube A is positioned in a reservoir sample so that when the proportioning pump E is operating the biological sample which may be blood, urine, or any other biological fluid is fed to a junction coupling means 24. The junction 24 has three exits. One exit is coupled by conduit or tube 25 to an inlet of a control valve 26, which forms part of the set of control valves C. Another outlet of the junction 24 is coupled by tube 27 to an inlet of a control valve 28, and the final outlet of the junction 24 is coupled by means of tube 29 to an inlet of a control valve 30. According to the requirement of the concentration of the sample to be used in the test being performed, all of the valves 26, 28 and 30 can be positioned to receive input samples. The valves can also be rotated to an alternate position where the sample is mixed with an appropriate diluent so that in all cases the volume of flow of fluid coming out of junction F is constant. This is desirable so that a uniform amount of air can be added in with the fluid through tube 11 so that a bubble pattern can be maintained. One of the reasons for inserting the bubbles in the stream is to produce a uniform segment of the sample during the analysis.

The free end of the diluent tube B is placed in a suitable diluent reservoir, such as an isotonic solution of an acetate buffer, PH^5 which because of its acidity will not accumulate carbon dioxide, neither will it cause precipitation nor interfere with any procedures normally performed in a clinical chemical laboratory. The stream of diluent is fed to a junction 31 which has three exits. One of said exits is coupled by conduit 32 to an inlet of valve 26. Another of said exits is coupled by conduit 33 on an inlet of valve 28 and still another of said exits is coupled by conduit 34 to an inlet of valve 30.

As previously mentioned, according to the setting of the control valves 26, 28 and 30, either the sample can be supplied to the tubes 13 through 15, or a stream of diluent can be supplied thereto. It is noted, however, that during the test one or the other is normally always flowing through the three tubes so that a constant volume stream of diluted sample is supplied to the exit of junction F. Therefore, it can be seen that the dilution of the sample stream can be varied for a particular test without disconnecting and changing the tubing. In one particular example, it is desirable that a 0.69 milliliter per minute flow rate be allowed at the exit of junction F. In order to produce such a milliliter rate of flow the tube 15 is of a diameter to permit 0.43 milliliters of fluid to pass therethrough per minute, tube 14 permits 0.16 milliliter per minute, and tube 13 permits 0.10 milliliters per minute. The proportional pump is a conventional pump and one such pump is described in U.S. Pat. No. 2,893,324. The tubes passing through the pump are flexible so that as the rollers associated with the pump pass thereover, the fluid is drawn from the sample side of the pump and passes out on the opposite side of the pump. At junction 36 the diluted sample can be mixed with a first reagent coming in tube 12 and air bubbles can be inserted into the stream by means of tube 11 to produce an air-segmented stream. A carbon dioxide trap 35 is associated with the tube 11 for removing any carbon dioxide which may be present in the airstream. The stream S1 can therefore, be formed by combining the aqueous solutions

flowing through tubes 13, 14 and 15, which contains the sample, with a reagent if desired, which would be flowing in tube 12, and air for segmentation which would flow through tube 11. The type of reagent which is combined with the sample depends on the particular sample being analyzed and the test being run.

From junction 36 the combined sample and reagent is passed through a mixing coil 37 wherein such are mixed together. After leaving the mixing coil 37 the main stream then passes through a distribution valve 38 associated with the first treatment circuit G. The valve 38 has four exits and when the valve is positioned so that the main stream flows out the lower exit through conduit 39 such then passes through a mixing coil 40 followed by a conventional air trap 41 which removes the liquid through tube 42. The gas or air is recirculated through tube 43, valve 44, conduit or line 45, and reenters the pump through tube 18. This gas is then fed back into the analyzer through tube 18 where it is mixed at junction 46 with a reagent coming in through tube 19 in the mixing coil 47 to produce a segmented stream. From the mixing coil 47 the stream flows in an inlet of valve 48. The valve 48 can be positioned so as to direct the stream through two mixing coils 49 and 50, respectively, if so desired.

Assuming that it is desired to analyze the stream after such passes through the mixing coils 49 and 50, such then flows through the double mixing coil 52 into the inlet of valve 53 and may go directly through conduit 54 to an inlet of an exit valve 55 bypassing a pair of heating baths 56 and 57, if so desired, and then passes into the flow cell 23 in the colorimeter J where such is analyzed and the results of such analysis recorded on a recorder 58. It is to be understood that the valves 53 and 55 can be so set as to direct the sample being analyzed to various other components or treatment stations within the analyzer.

Also, depending on the test being run a second reagent could have been entered into the main stream through conduit 20 and the valve 59 interposed between the two mixing coils 49 and 50. If it is not desired to feed the reagent which is being supplied to line 20 into the main stream, then the valve 59 can be turned so that the reagent will flow to waste through the conduit 60.

The above is a description of analysis of a gas which is taken off in the air trap 41. The following is a description of the analysis of a liquid portion of the main stream of sample wherein the valve 38 is positioned to direct such through the remainder of the analyzer. Such is accomplished by turning the valve 38 so that the main stream can be fed to one of the three output tubes 61, 62 or 63. The output tube 61 leads into an exit valve 64 which permits the main stream to bypass the first treatment circuit which includes a plurality of treatment stations or modules. When valve 38 is positioned so that the main stream is fed through conduit 62 such is supplied to a dialyzer 65 where the sample is passed over a membrane into a recipient stream generated by tubes 16 and 17 of the proportion pump E which are, in turn, connected through valve 66 and tube 67 to the dialyzer 65. Any suitable aqueous reagent can be added through line 16 and air segmented by a air flowing through line 17, depending on the particular test being run. The purpose of the dialyzer 65 is to remove the proteins through line 68 from the main stream so that subsequent tests can be performed thereon. It is noted that valve 66 can be rotated so as to direct the stream S2 to various other areas of the testing apparatus. The valve 38 can be turned so that the main stream flows through tube 63 into an incubating bath 69 from where the main stream can flow by means of valve 70, either directly to the exit valve 64 into a subsequent analyzing or treatment circuit, or such can flow from valve 70 through tube 71 into another dialyzer 72 and then fed to the exit valve 64.

From the exit valve 64 the main stream is fed through conduit 71 into another treatment circuit H, such as illustrated in broken lines. An input valve 73 is provided at the entrance of the treatment circuit H for directing the main stream to various treatment stations within the circuit. The valve 73 can be so positioned so as to direct the main stream to flow directly to junction 74 or such can be rotated so as to direct the flow through tube 75 where additional reagents can be added thereto by means of conduit or tubing 48*a* and 59*a*, respectively. After the main stream reaches the junction 74, it then passes as previously mentioned, through the double mixing coil 52 and exits to a third treatment circuit shown in broken lines and identified by the reference character I. It is noted that the main stream coming into the second treatment circuit H could have bypassed all of the treatment stations wherein by means of tubing 76 extending from an exit of the valve 73 to a junction 77 which is also coupled to the output of the double mixer 52.

As the main stream leaves the treatment circuit H it is then fed into the treatment circuit I, wherein such can be heated by either of the heating baths 56, 57 or 69 by merely rotating the valve 53 to the desired exit. The output tube 78 leads form an exit of valve 53 to the input of the heating bath 69 and exits through lead 79 to the output valve 55 of the treatment circuit I. The valve 53 can also be rotated so as to feed the main stream to the heating bath 56 which exits to the exit valve 55 or to the heating bath 57 which also exits to the exit valve 55. The valve 55 then permits the main stream to flow directly to the colorimeter J where the analysis is performed on the sample and the results of such is recorded on the recorder 58. All of the heating baths 56, 57 and 69 can be bypassed if so desired, by turning the valve 53 to the upright position and allowing the main stream to flowdirectly from valve 53 to exit valve 55 through tube 54.

An important feature of the subject invention is that by using various size tubes, such as illustrated by tubes 13, 14 and 15 one can aliquot the sample according to the requirement of tests being performed. The tube 22 is merely used to supply water to the sampler, which is not shown. Tube 21 is the return flow from the flow cell which permits the main stream to discharge its waste. Tubes 16 and 17 can also be used for supplying segmented streams of reagent to an input of valve 66 and such can be rotated to direct the flow to various treatment stations within the circuit G, or to the tube 80 coupled to the mixing coil 37.

It can be seen from the foregoing that a wide variety of treatments and treatment sequences are possible. The versatility of the manifold can be further extended by using the diluent as a fifth reagent, and by adding a fluorometer to the measuring circuit with a selective valve in front.

Since all connections are permanent the use of nipples is largely discontinued. Wherever possible transmission goes through Teflon connected to glass or male luer tip on valves. Elsewhere, the transmission tubing is only cyclohexanone-sealed sleeving. A more smooth transmission is achieved in this way. Reagents are clamped to the right side of the system in the usual way, and rapid wash between samples is possible due to the rigidity of the system.

The valves should be gas tight and inert so as not to be damaged by material flowing therethrough. Suitable valves are manufactured by the Hamilton Company of Whittier, California and are referred to as Hamilton inert valves.

In operation of the manifold it must be assumed that the system has been washed with water after the last run. The position of each individual valve is to be determined from a valve setting guide provided for a particular test. A suitable wash detachment is connected to the manifold on the proportional feeding pump and is started at regular speed. After a quick check of the flow for determining if satisfactory bubble pattern is present the rapid wash switch on the pump is flipped on. After the wash has taken place the reagents attachments are then again hooked to the tubes leading into the proportional pump E. Under no circumstances should the valves be turned while the pump is in operation, although only a few valve setting combinations may cause a pressure build-up.

Except in cases of extremely high or extremely low aspiration rates values considerably above or below the normal standard range, evaluation can be made without tampering with

the sample. For high valves that would normally be obtained by dilution of a specimen, repetition can take place at lower aspiration rate and with a corresponding set of standards higher than those normally used. For lower values the aspiration rate is increased, and standards of lower concentration are used. In some cases it is also possible to dilute the main stream with the aid of streams S2, S3 and S4, if these are not already employed. This, however, is mostly applicable in cases of grossly elevated values.

While a preferred embodiment of the invention has been described using specific terms, such description is for illustrative purposes only, and it is to be understood that changes and variations may be made without departing from the spirit or scope of the following claims.

What is claimed is:

1. In combination with an automatically operable analyzer, a system for concomitantly consolidating a stream of diluent with a stream of test sample so that a constant volume stream of sample of a predetermined concentration can be produced for analysis by said analyzer comprising; a sample tube carrying a stream of samples; a first junction means, said sample tube having an outlet connected to said first junction means; a diluent tube carrying a stream of diluent; a second junction means, said diluent tube having an outlet connected to said second junction means; at least three control valves each of said valves having at least a pair of inlets and an exit; conduit means connecting said first junction means to an inlet of each of said valves; conduit means connecting said second junction means to another of said inlets of each of said valves; at least three tubes each having a different internal diameter, each of said three tubes having one end connected to an exit of a respective valve, means for setting each of said valves to provide communication from a particular one of said inlets to said exit; pumping means coupled to said three tubes for causing a continuous stream to flow through each of said three tubes in a volume in accordance with the particular internal diameter thereof; a third junction means, each of the other ends of said three tubes being coupled to said third junction means; an exit tube coupled to said third junction means receiving a constant volume stream of sample of a predetermined concentration from said third junction means whereby said concentration of said constant volume stream can be varied by changing the setting of said valves; and said automatically operable analyzer being coupled to said exit tube for analyzing said stream flowing therethrough.

2. The combination as set forth in claim 1, wherein said analyzer includes a plurality of treatment circuits, each of said treatment circuits including a plurality of treatment stations and a distribution valve, said distribution valve being operable so as to selectively direct said stream to a particular treatment station.

3. The combination as set forth in claim 2, wherein said treatment stations in one treatment circuit include a dialyzer, an incubating bath and a debubbler.

4. The combination as set forth in claim 2, wherein one of said treatment circuits includes a mixing coil connected so that said stream flows therethrough when said respective distribution valve is set to a particular setting; a conduit for a stream of reagent; a valve having an inlet coupled to an outlet of said reagent conduit and having a plurality of exits, at least one of said exits communicating with said mixing coil for mixing said reagent with said stream of sample when the last-mentioned valve is set in one position.