United States Patent [19]

Bagshawe et al.

[11] **3,784,826**

[45] **Jan. 8, 1974**

[54] **APPARATUS FOR ANALYSING CONTINUOUSLY DISCRETE BIOLOGICAL LIQUID SAMPLES**

[75] Inventors: **Kenneth D. Bagshawe,** London; **Derek N. Marchant,** Hassocks, both of England

[73] Assignee: **The Hayward Foundation,** London, England

[22] Filed: **Feb. 24, 1971**

[21] Appl. No.: **118,426**

[30] **Foreign Application Priority Data**

Mar. 3, 1970 Great Britain 10,023/70

[52] **U.S. Cl.** ..... **250/106 SC**

[51] **Int. Cl.** **G01t 1/16**

[58] **Field of Search** ..... 250/71.5 R, 106 SC; 23/230 B, 253 R; 356/39

[56] **References Cited**

UNITED STATES PATENTS

3,614,434 10/1971 Horwitz ..... 250/71.5 R

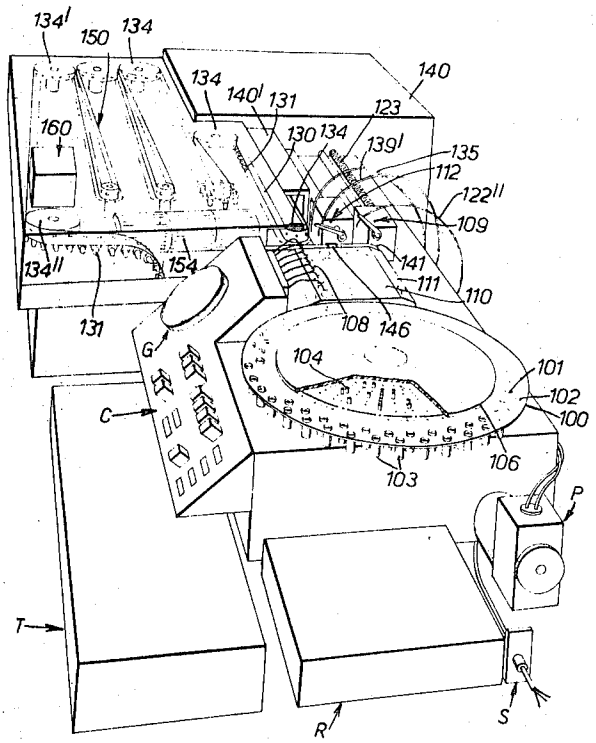
Primary Examiner—James W. Lawrence
Assistant Examiner—Davis L. Willis
Attorney—Pennie, Edmonds, Morton, Taylor & Adams

[57] **ABSTRACT**

Analysis apparatus primarily for carrying out biological analyses using radioimmunoassay techniques includes a turntable disc for carrying a plurality of specimens. A delivery arm delivers successive samples to a row of dilution containers and simultaneously supplies a diluent. A transfer arm controlled by a code on the turntable disc picks a selected diluted sample and transfers it to one of a long series of incubation chambers each of which contains a reagent. A second reagent is added at the time of transfer and the mixture is incubated prior to removal by an appropriate device. After removal the active constituents are filtered and measured quantitatively by a counter.

The pumps for transfer of liquids are peristaltic and where a sample has to be drawn up incorporate an integral bellows.

26 Claims, 28 Drawing Figures



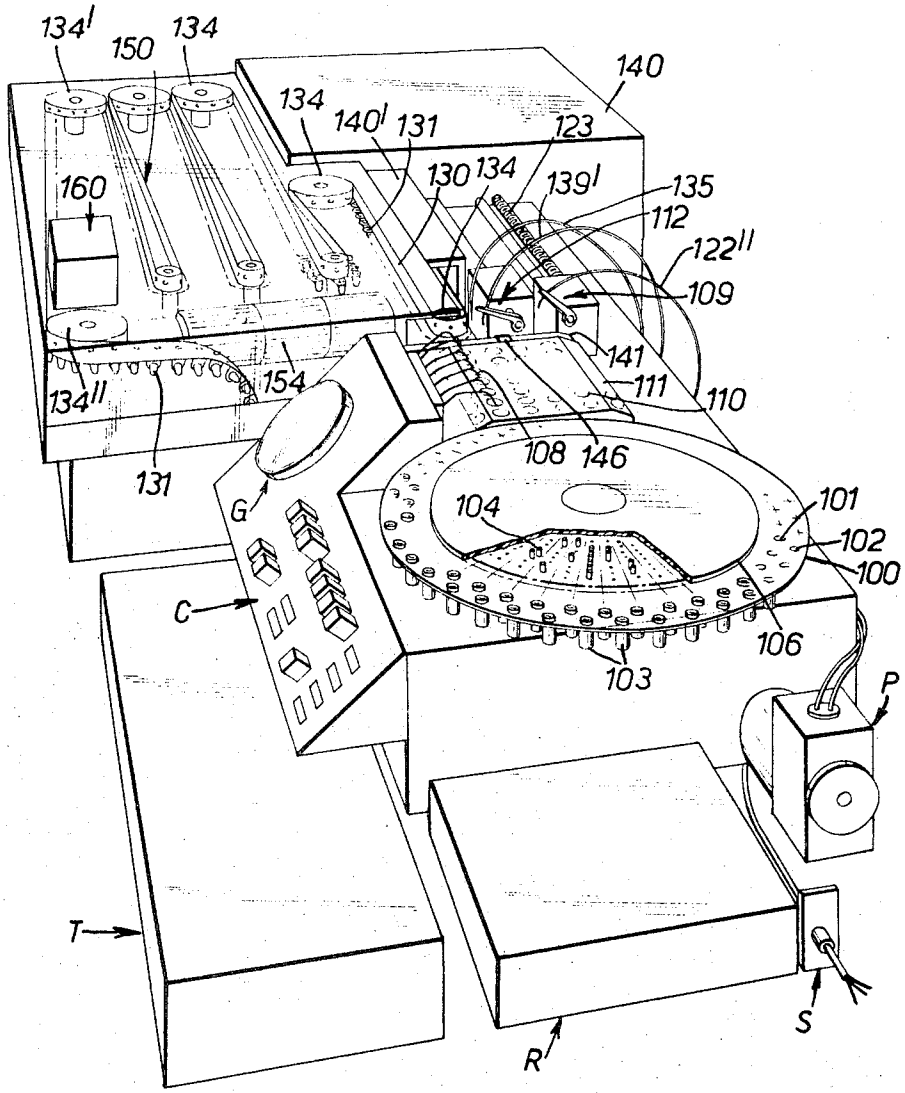


FIG. 1.

INVENTOR
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

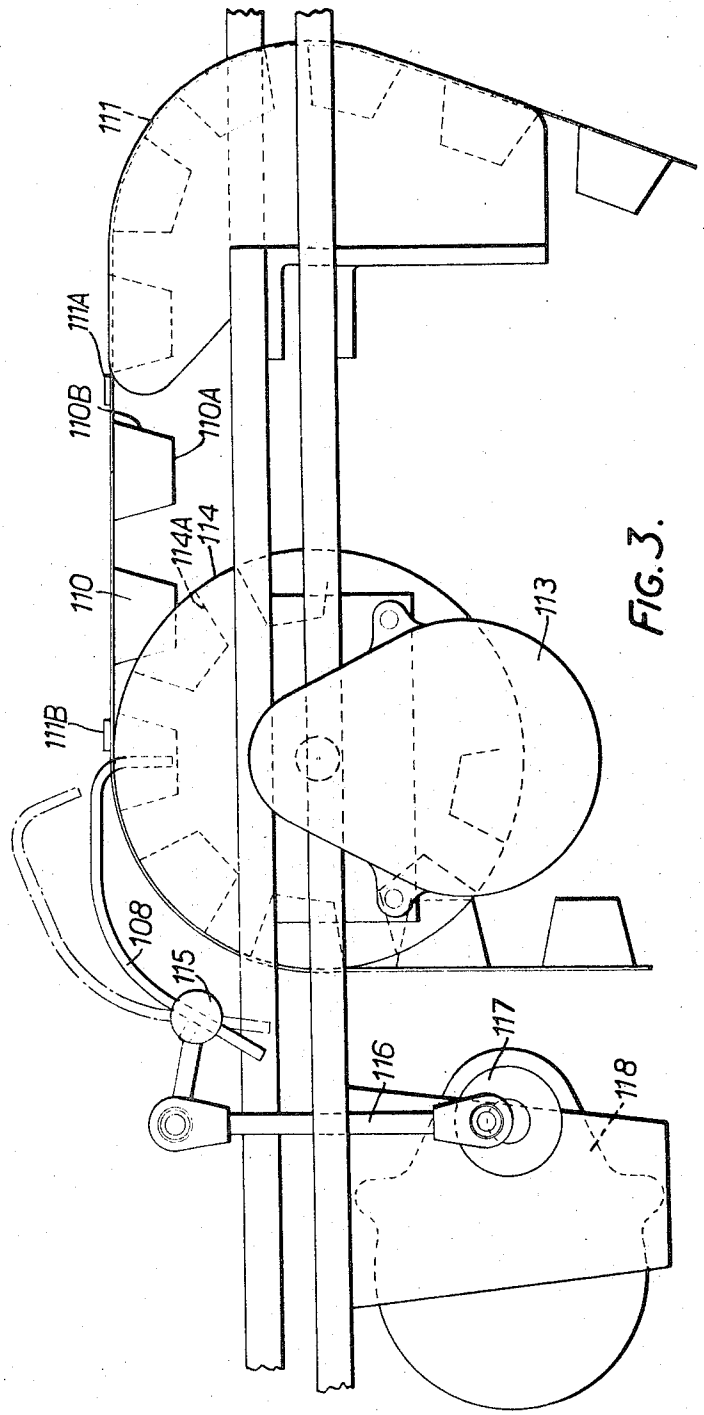


FIG. 3.

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Eidmondt, Morton, Taylor & Adams
ATTORNEYS

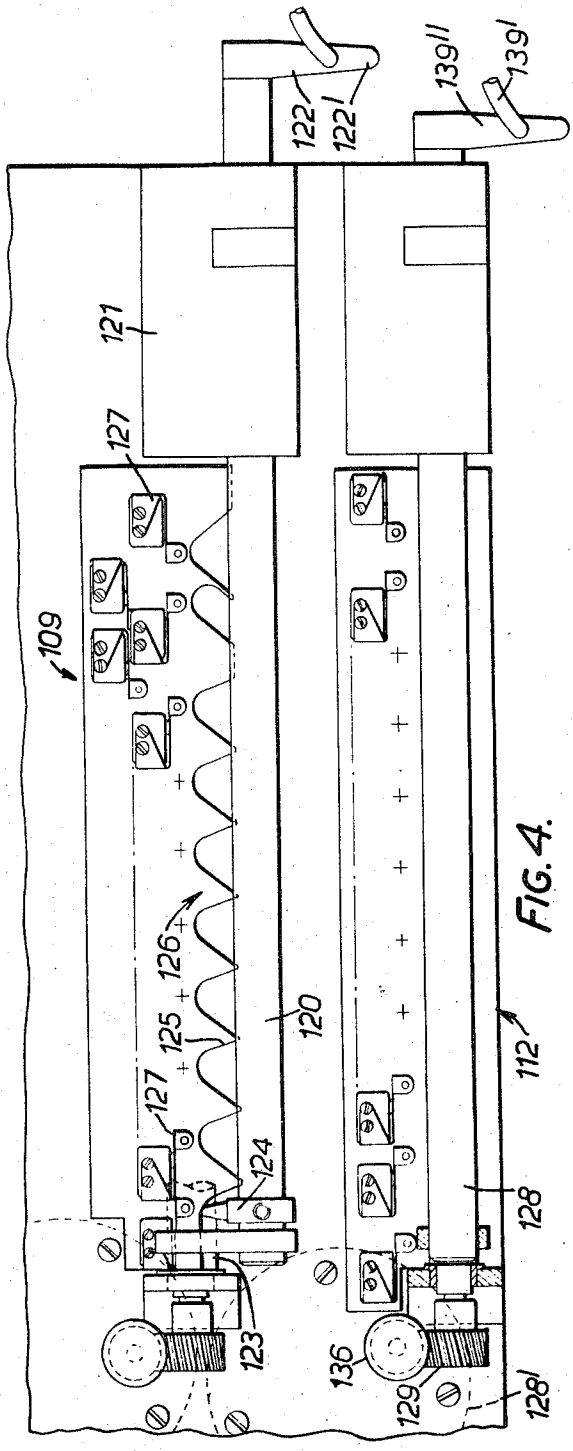


FIG. 4.

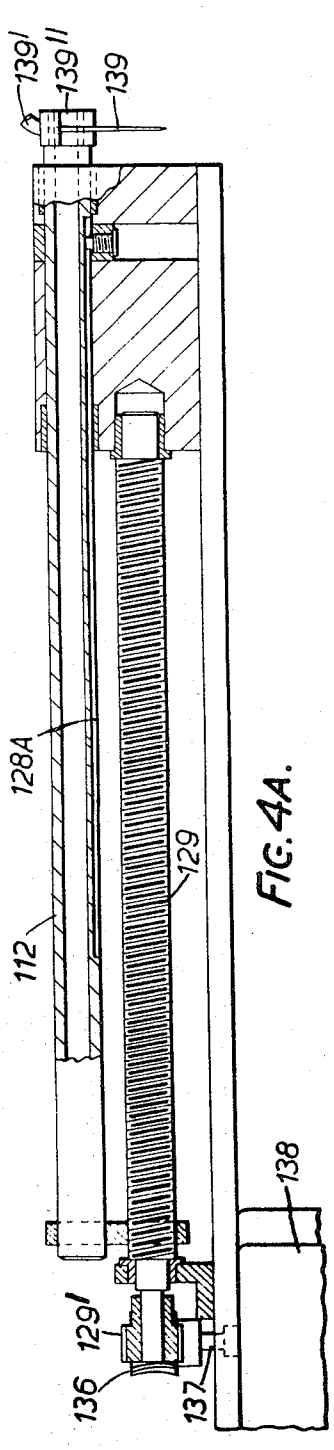


FIG. 4A.

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Cushman, Edmunds, Morton, Taylor & Adams
ATTORNEYS

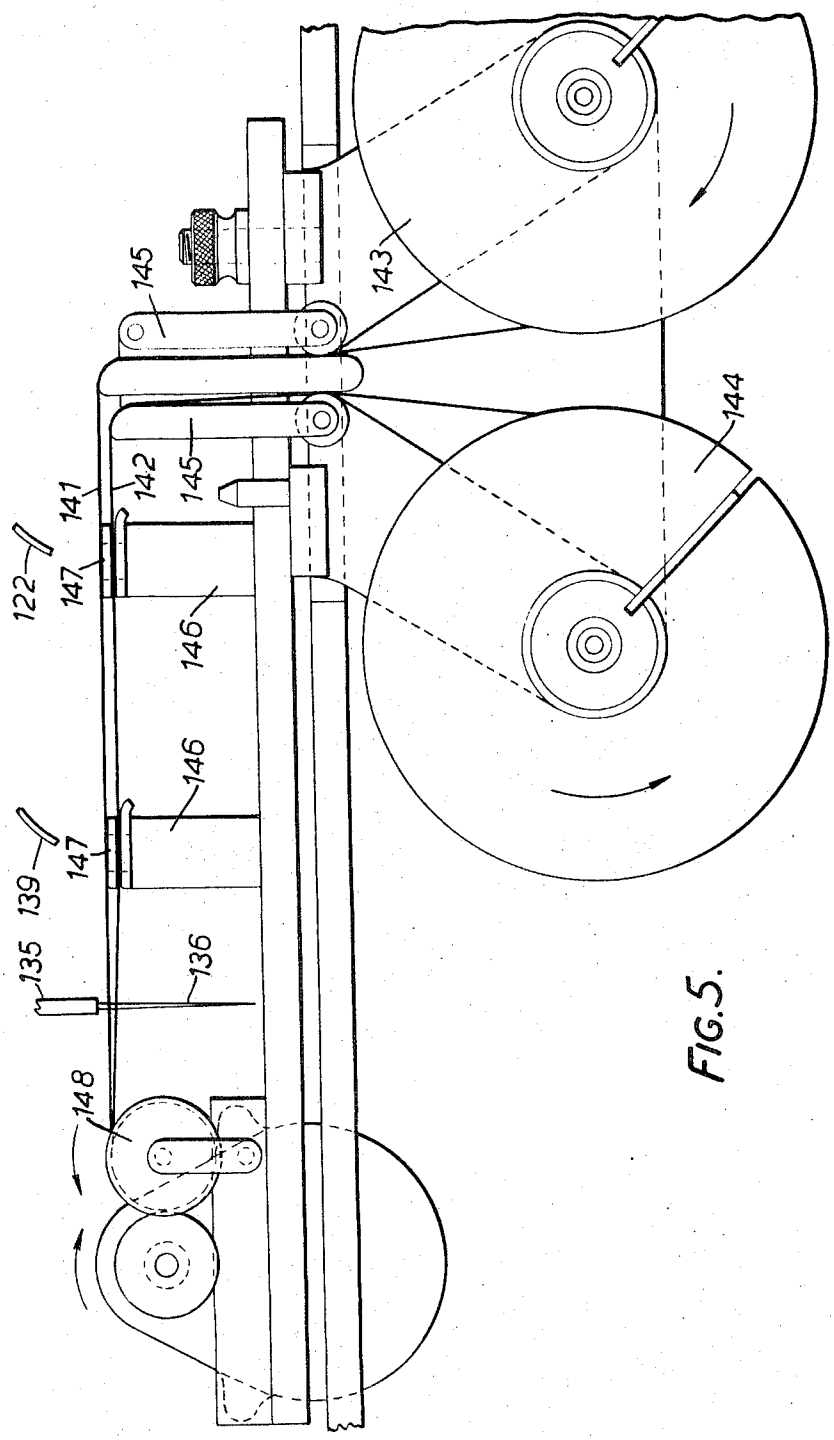


FIG. 5.

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

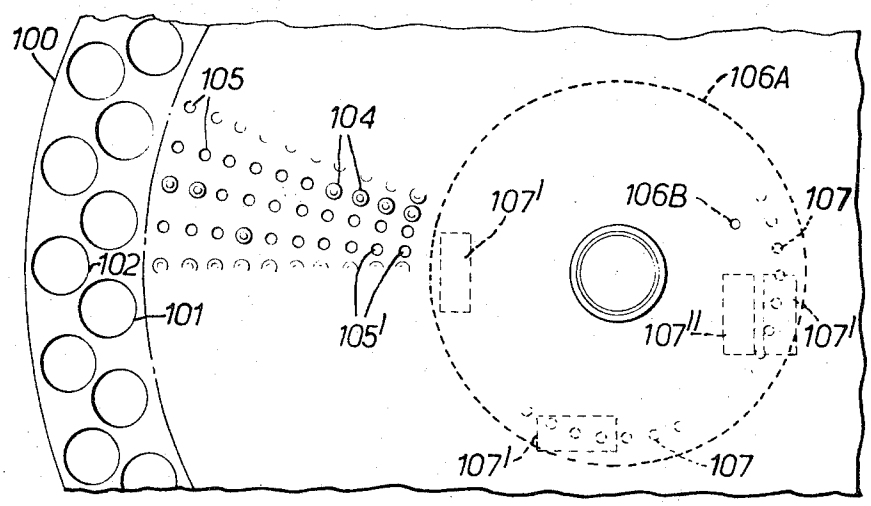


FIG. 2.

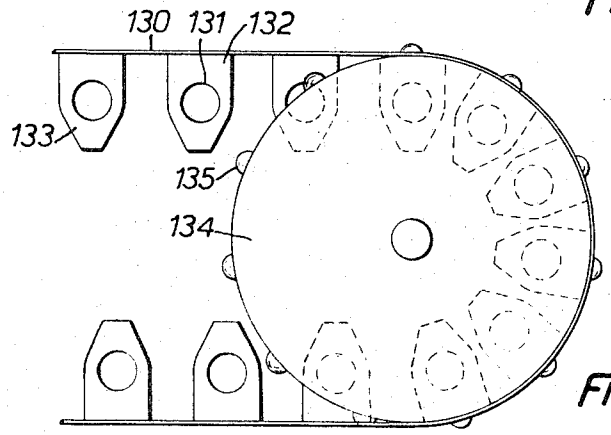


FIG. 6.

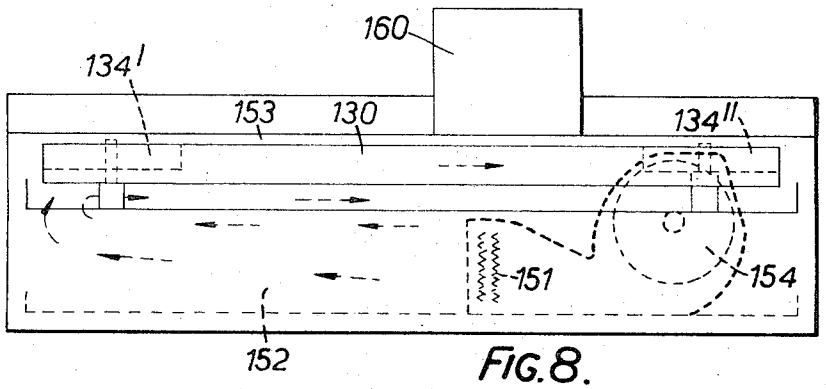


FIG. 8.

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

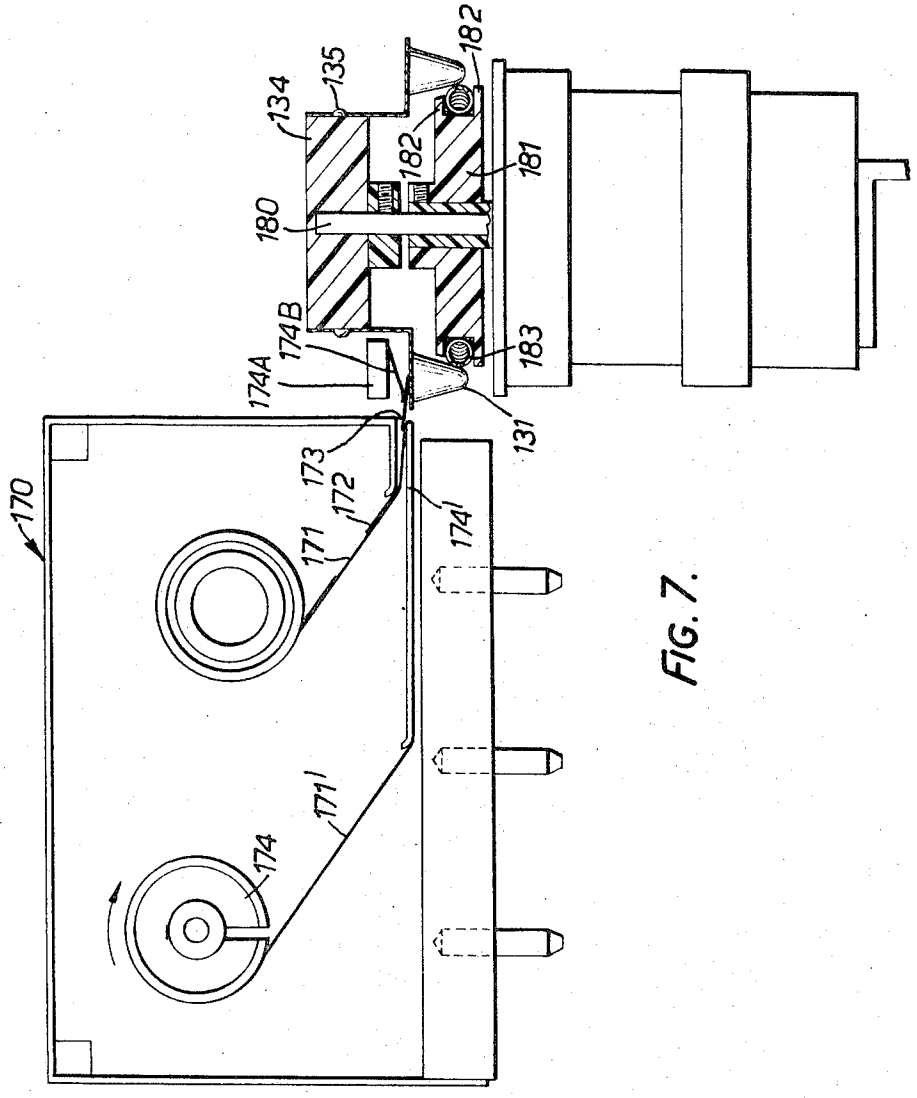


FIG. 7.

INVENTORS
KENNETH D. BAGSHAWE.
DEREK N. MARCHANT.
BY Dennis, Edmonds
Morton, Taylor & Adams
ATTORNEYS

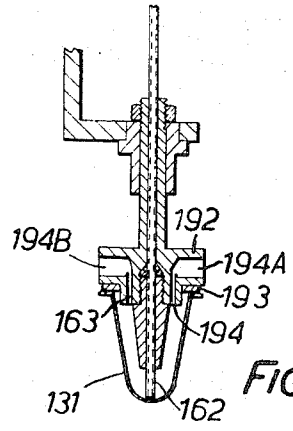


FIG. 9A.

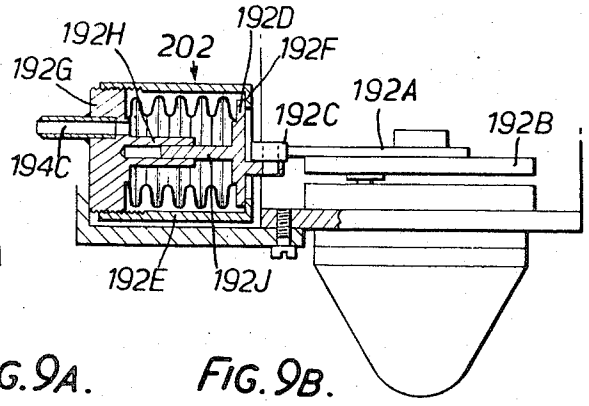


FIG. 9B.

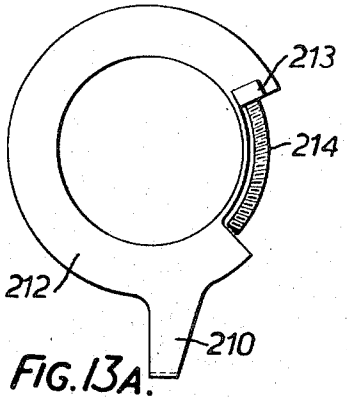


FIG. 13A.

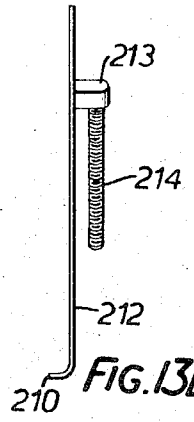


FIG. 13B.

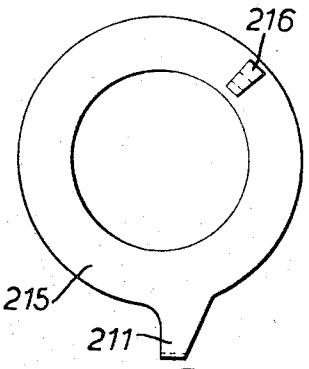


FIG. 13C.

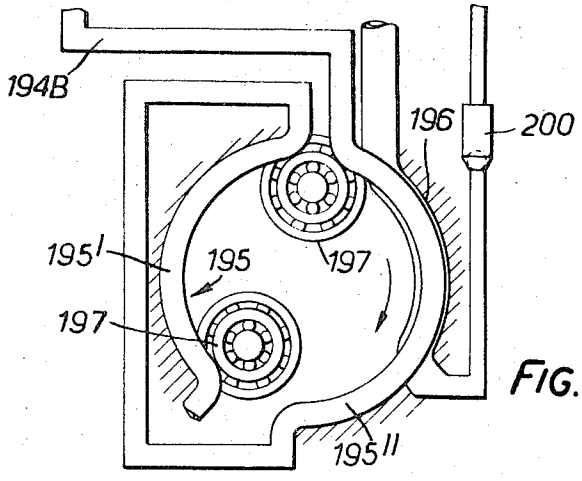


FIG. 9C.

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Cennie, Edmonds, Morton, Taylor & Adams
ATTORNEYS

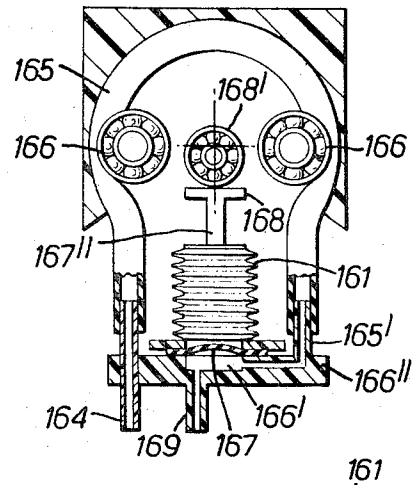


FIG. 10.

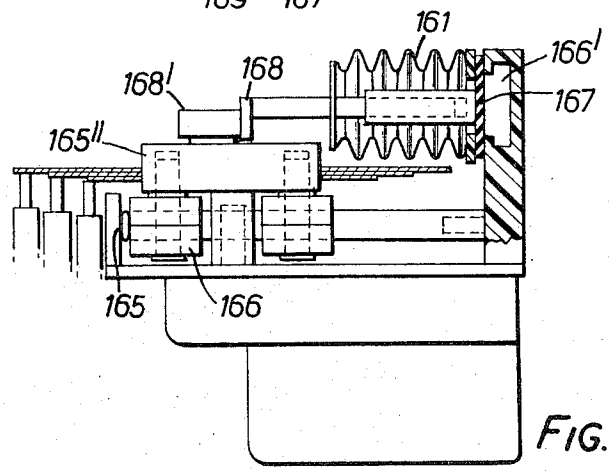


FIG. 11.

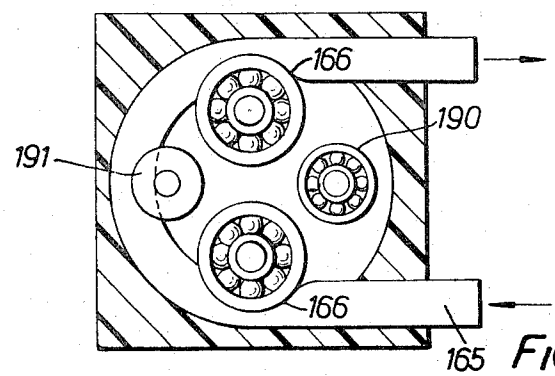


FIG. 12.

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

FIG.14A	FIG.14D	FIG.14G
FIG.14B	FIG.14E	FIG.14H
FIG.14C	FIG.14F	FIG.14J

FIG. 14

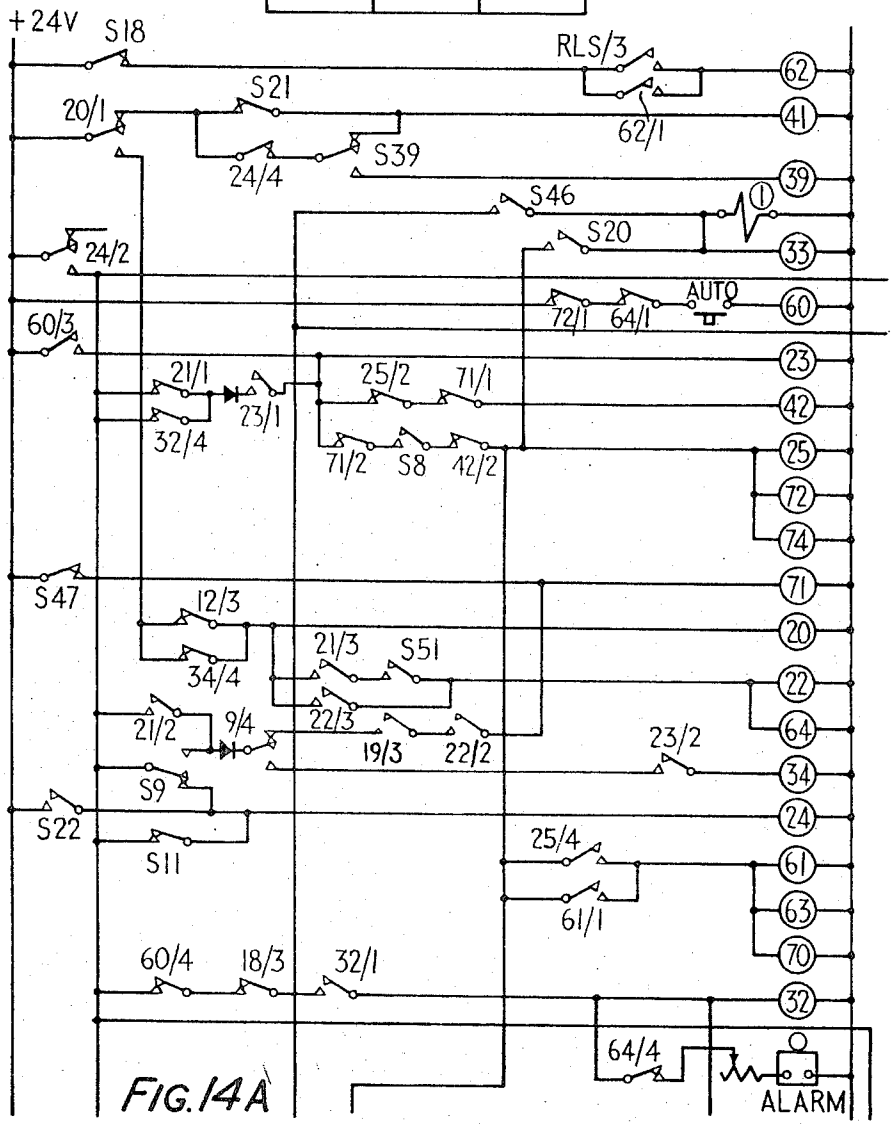
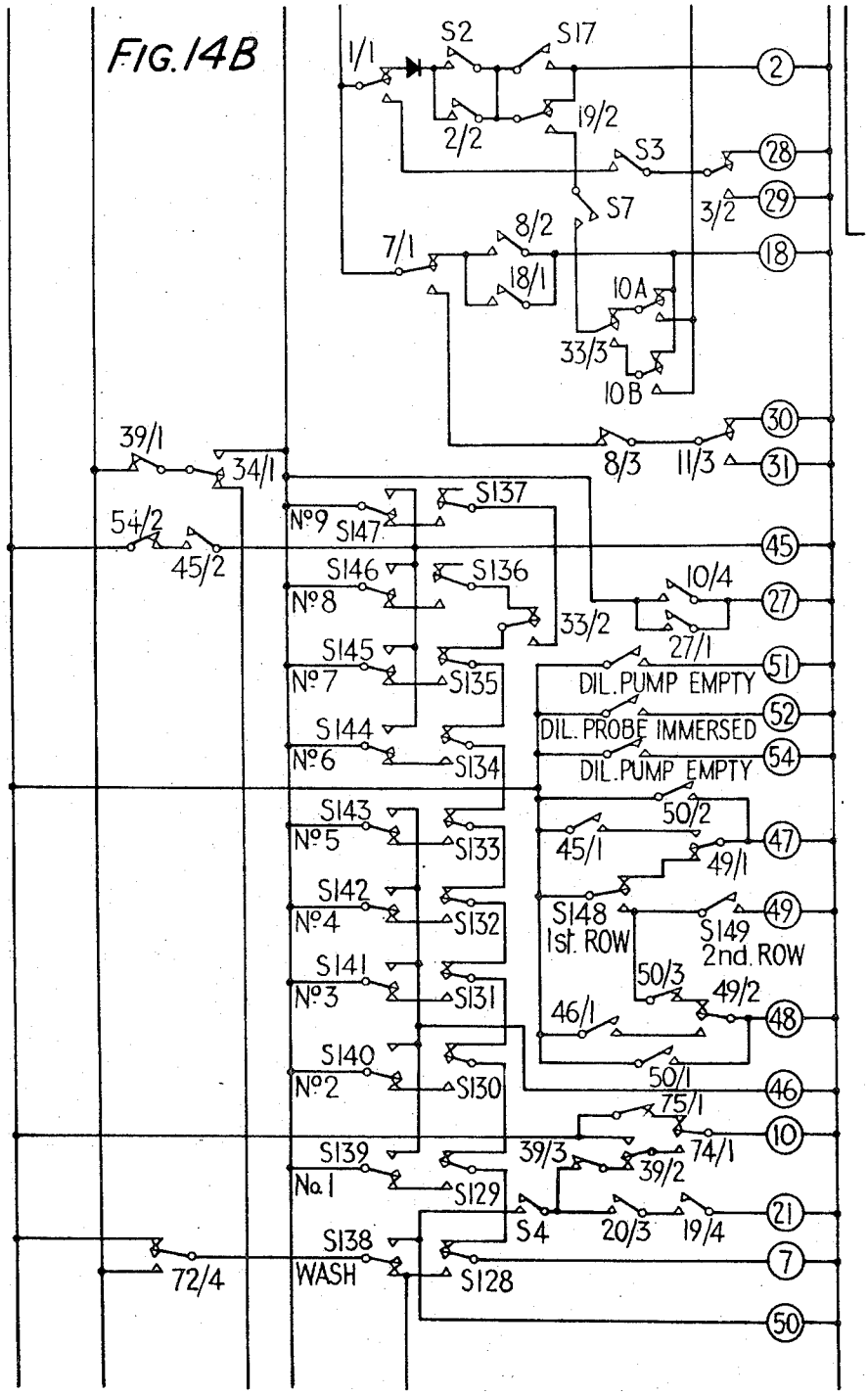


FIG.14A

INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennie, Edmonds, Morton, Taylor & Adams
ATTORNEYS

FIG. 14B



INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

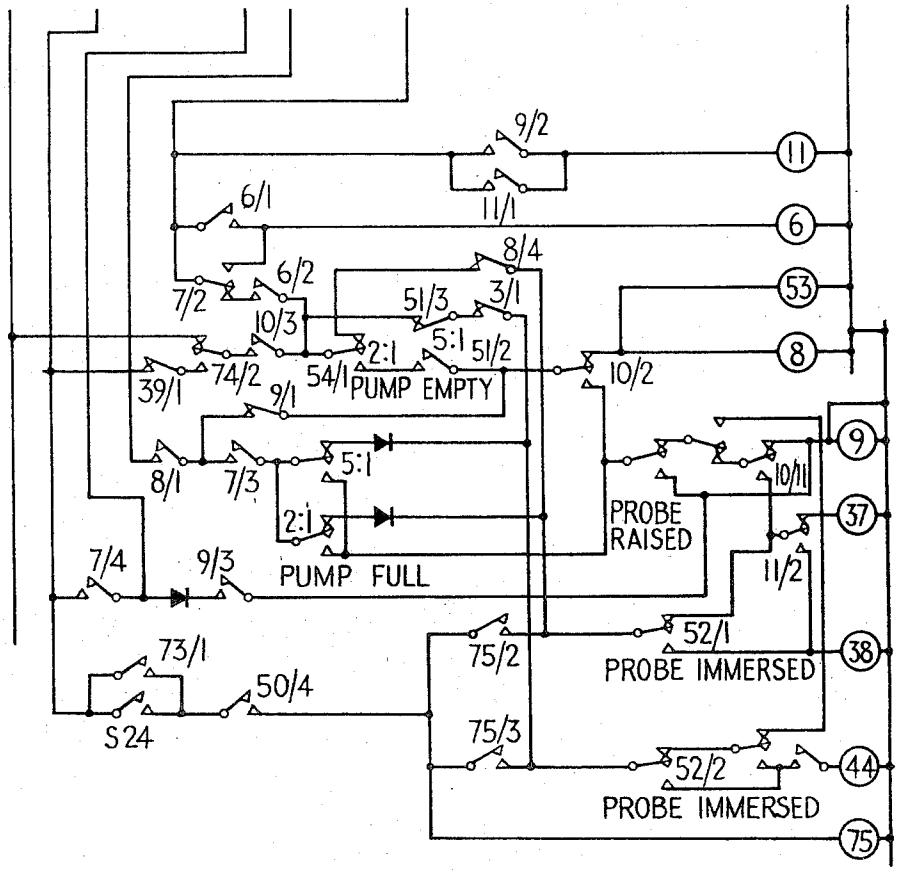
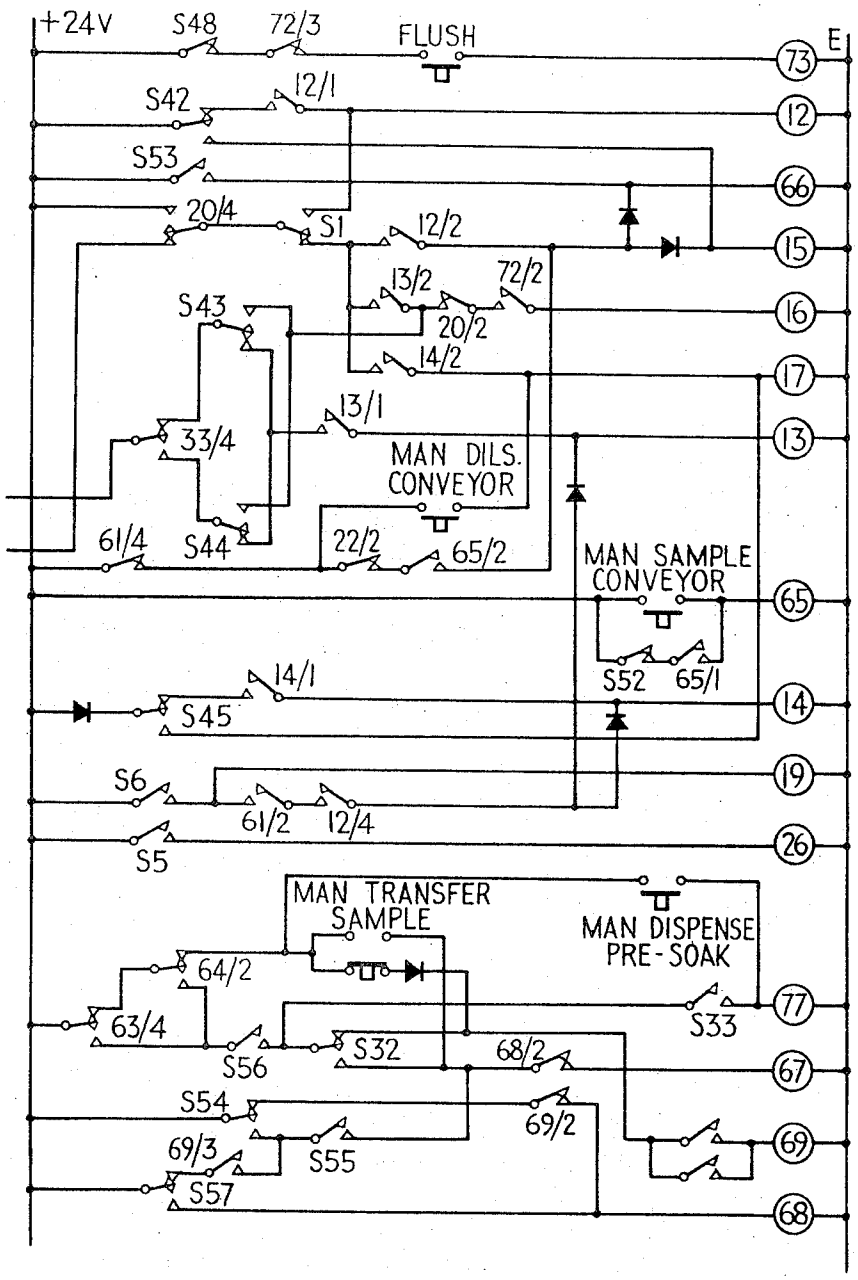


FIG. 14C

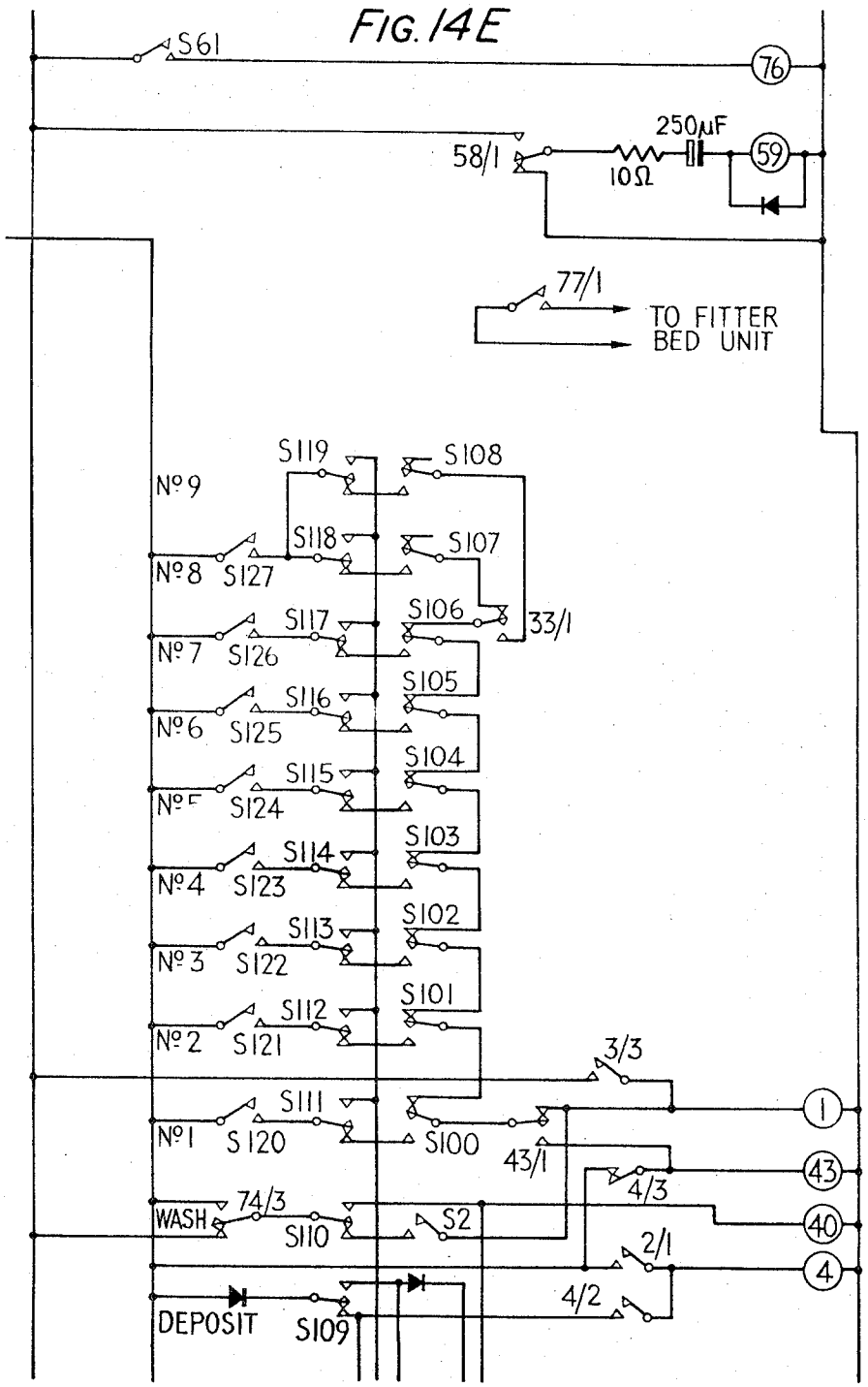
INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennie, Edmonds,
Morton, Taylor & Adams
ATTORNEYS

FIG. 14D



INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

FIG. 14E



INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

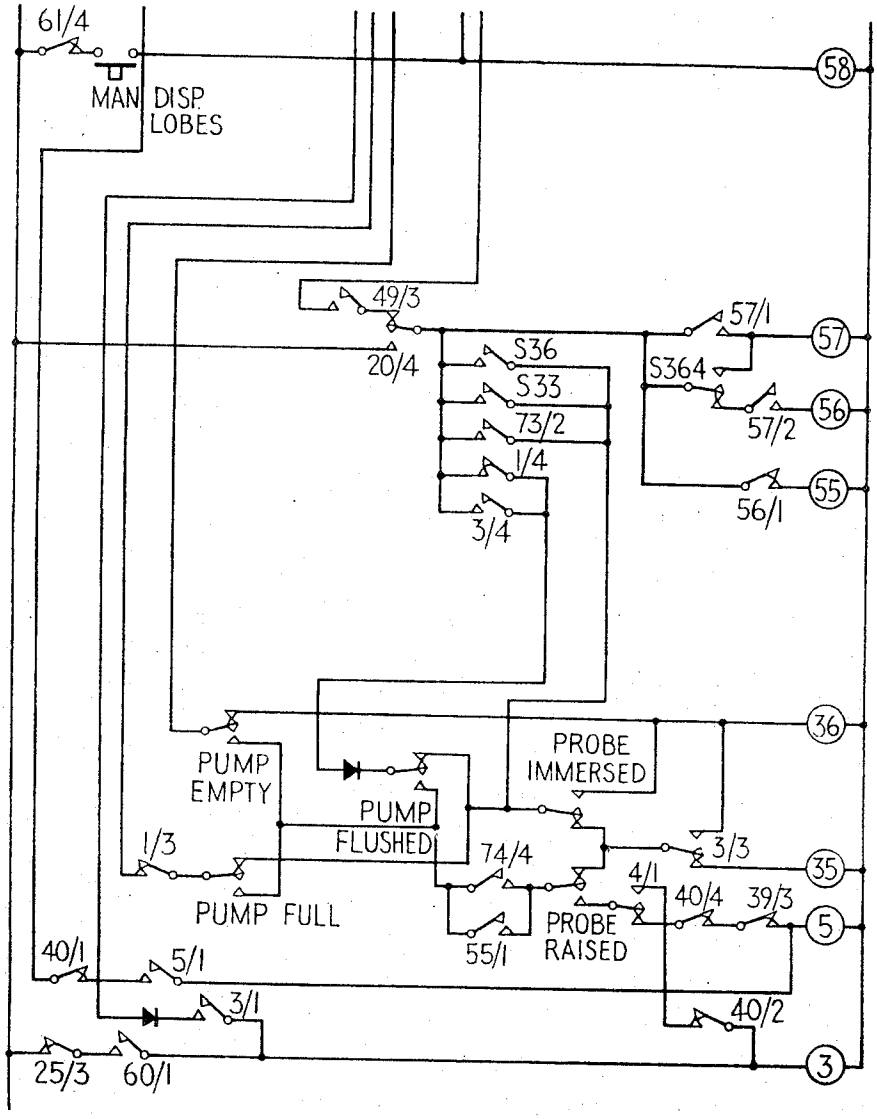
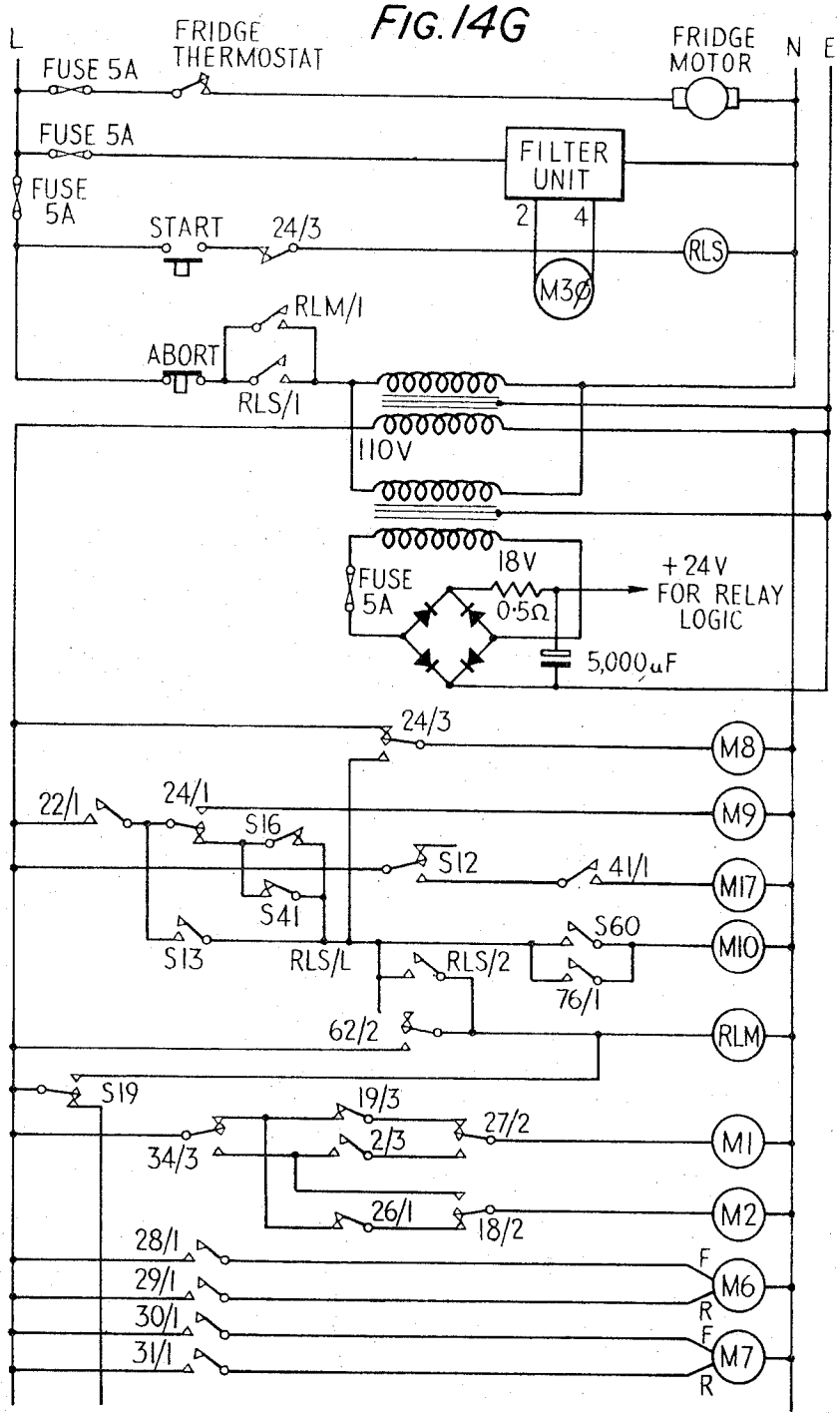


FIG. 14F

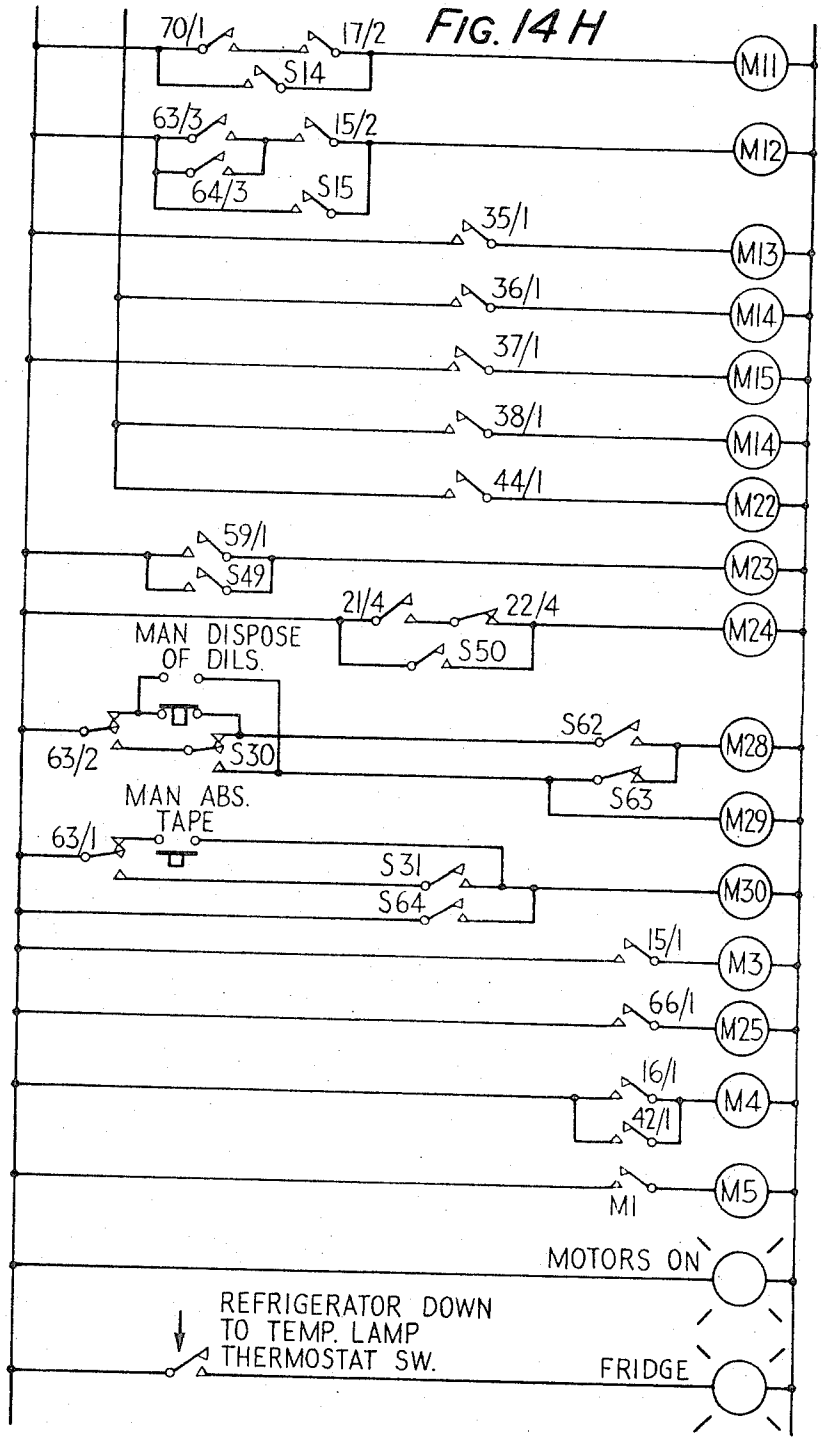
INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

FIG. 14G



INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

FIG. 14H



INVENTORS
KENNETH D. BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edwards, Morton, Taylor & Adams
ATTORNEYS

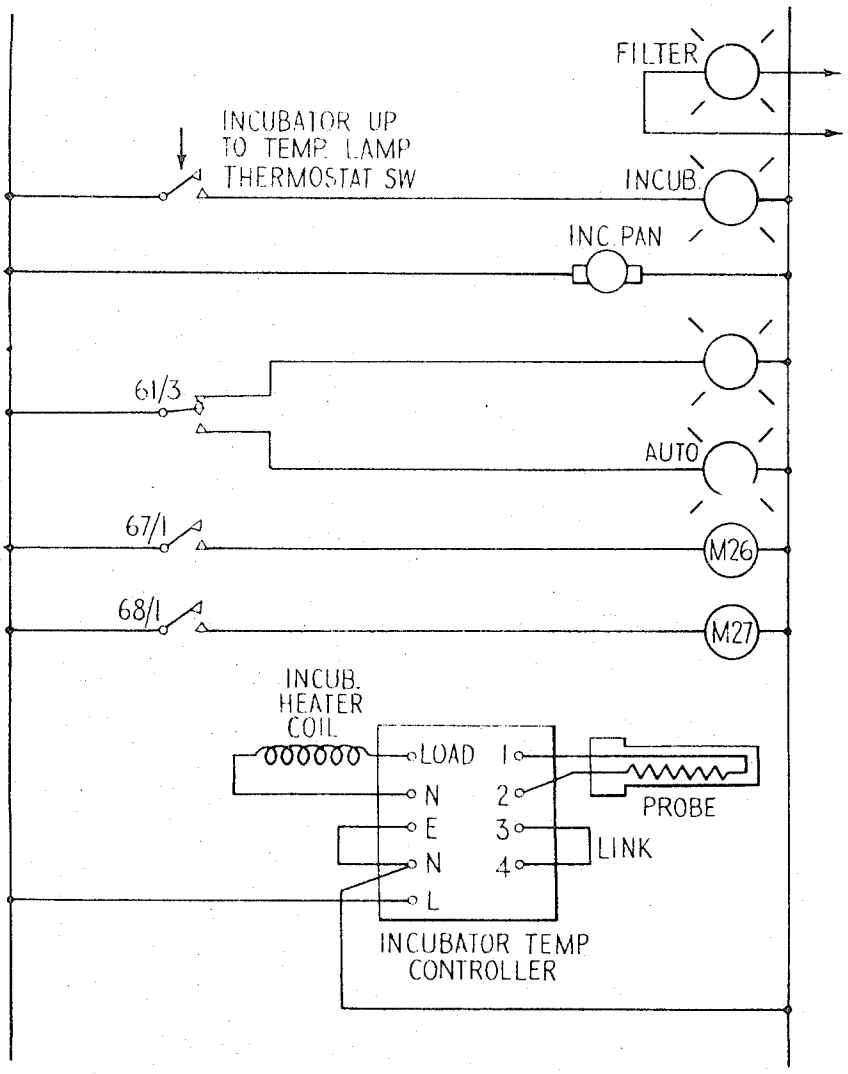


FIG. 14J

INVENTORS
KENNETH D BAGSHAWE
DEREK N. MARCHANT
BY Dennis, Edmonds, Morton, Taylor & Adams
ATTORNEYS

APPARATUS FOR ANALYSING CONTINUOUSLY DISCRETE BIOLOGICAL LIQUID SAMPLES

The invention relates to an analysis method, apparatus and system.

Proposals have already been made for the analysis of biological samples on a continuous flow basis with a view to speeding up analytical procedures and with a view to reducing the unit cost of analysis. However, such previously proposed apparatus has met with difficulties owing, at least in part, to carry-over from one sample to the next within the communication passages of the apparatus.

Numerous analysis methods for biological samples are available of which radioimmunoassay has particular application where the sample includes, or may include hormones, enzymes or other substances produced by normal or cancerous cells. The technique of radioimmunoassay serves to measure accurately the quantity of a specific species of a protein and/or a specific species of a polypeptide in a sample, for example urine, blood or plasma, by reaction with specific anti-bodies produced in an animal in response to injections with the protein or polypeptide to be measured. Further, isotopically labelled protein or polypeptide of the specific species to be measured is added to the sample and this competes with the specific protein or polypeptide of the unknown sample for binding sites on the antibody. In order to measure the degree of binding with the antibodies it may be necessary to add a further antibody or a carrier particle. Separation of isotopically labelled protein or isotopically labelled polypeptide bound to an antibody from corresponding substances which are not bound can be effected by filtration, centrifuging or electrophoresis.

It is possible to measure the presence quantitatively of many proteins even in very low concentrations, and this reduces the quantity of costly antibodies required, but, where large numbers of tests are required, the time consumed in carrying out the tests is excessive and testing of large sections of the population by way of screening, becomes impossible.

According to the present invention, there is provided analysis apparatus comprising means for successively delivering discrete biological samples to successive containers at a station at which each sample is diluted to produce a plurality of diluted samples, means for diluting the samples at the dilution station, means for transferring a selected said diluted sample to an incubation container, an incubator for incubating the selected diluted sample in the container and analysis means for analysing components of the diluted incubated sample.

According to the present invention, there is further provided liquid analysis apparatus incorporating a plurality of remotely controlled peristaltic pumps for delivering and/or transferring quantities of liquid to and/or from containers of the apparatus, at least one of the pumps incorporating bellows means, operable at the end of each delivery cycle of the pump to produce a suck-back action preventing the formation of drips.

An embodiment of analysis apparatus in accordance with the invention will now be described, by way of example, with reference to the accompanying diagrammatic drawings, in which:

FIG. 1 is a perspective view of analysis apparatus in accordance with the invention;

FIG. 2 is a plan view of a turntable for carrying original, undiluted samples and forming part of the apparatus shown in FIG. 1;

FIG. 3 is a side elevation of a device for disposing of unwanted diluted samples;

FIG. 4 is a plan view illustrating a specimen dilution arm and a sample selection arm;

FIG. 4A is a side elevation of the sample selection arm of FIG. 4;

FIG. 5 is a side elevation of a device for cleaning certain parts of the arms shown in FIG. 4;

FIG. 6 is a fragmentary plan view of an incubation container web and one of the pulleys on which it is mounted;

FIG. 7 is a side elevation of a device for capping the individual containers of the incubation container strip conveyor and part of the drive for the incubation container web;

FIG. 8 is a vertical section through an incubator of the apparatus;

FIG. 9A is a vertical section of an arrangement for removing the contents of successive incubation containers;

FIG. 9B illustrates a detail of the arrangement of FIG. 9A;

FIG. 9C is a diagram of an associated peristaltic pump;

FIG. 10 is a diagram illustrating a pump used for certain fluid supply and withdrawal operations in the apparatus;

FIG. 11 is a section of the pump illustrated in FIG. 10;

FIG. 12 is a section of another pump used in the apparatus;

FIGS. 13A to 13C illustrate a device for adjusting the operation of one of the pumps; and

FIG. 14 is a circuit diagram of the control system of the apparatus.

In outline, the apparatus as illustrated in FIG. 1 includes a turntable disc **100** or other carrier means which has two rings of apertures **101, 102** each containing a pot **103** or other specimen container which is preferably disposable but is, in any event, readily removable from the turntable disc. The turntable disc **100** has a plurality of sets of pegs **104** selectively engaged in holes, or notches, the rows of holes or notches extending radially inwardly from the rings of apertures **101, 102.** The position of the peg **104** in any given radial row dictates the required dilution or neat specimen from which a sample is taken. Each sample is withdrawn from its pot **103** by delivery means **109** and diluted to a series of dilutions in a row of depressions **110** or other dilution containers in a plastics band **111** and a selected diluted or undiluted sample is transferred by transfer means **112** to an incubation train **130** which includes a row of disposable plastics containers **131.** The incubation train is initially stored in a refrigerated compartment **140.** One reagent is already contained in each container **131** and another is added preferably simultaneously with transfer to the container **131,** and the biological reactions are allowed to proceed with the aid of thorough mixing by agitation at the time of transfer and for about three minutes thereafter. The incubation train then follows an elongate path through an incubator **150.** The length of this path through the incubator and the speed of the incubation train is such that the elapsed time from the addition of the reagents to

the separation of the constituent to be measured corresponds to the required incubation time (say 2 hours at 37° C), for the reagents and sample in question. In the embodiment disclosed, the incubation train is indexed forward at one minute intervals.

On completion of the incubation, the samples are removed from the containers **131** by an incubated-sample removal means **160** and the molecular complexes in the incubated material are separated into the antibody-bound and antibody-free phases either by filtration, centrifuging or electrophoresis as is conventional in radioimmunoassay techniques. In the preferred embodiment a vacuum filtration process is employed, the mixture being released on to a filter material by successively withdrawing the incubated sample from each container of the incubation train and washing out the whole of the contents on to the filter material by gelatin or other washing agent dispensed by the removal means **160.**

The filter bed material (not shown) moves past or through an isotopic counter and the whole bed, including sample solids, is passed to waste. The output of the isotopic counter is supplied to a pulse-height analyser (not shown) which, in turn passes its output to a rate meter. If desired, the signals from the rate meter are recorded on a chart recorder.

Preferably the output of the multiplication stage is fed via a scaler to a data processor which correlates the result with sample identification information and the selected degree of dilution in order to produce comprehensive digital information at a final print-out.

For any one analysis apparatus more than one disc **100** and set of pots **103** will be provided, since, when one set of samples is being processed another set is being loaded with fresh sample-containing pots.

Provision may be made, as will be described hereinafter in detail, for continuing the incubation stage of the analysis after the part of the apparatus upstream of the incubator has been shut-down. Since the incubator requires no supervision, an extension of the working day of the apparatus can be achieved.

Certain parts of the analysis apparatus and system will now be described in more detail.

Referring particularly to FIG. **1,** the specimens to be tested are arranged in the moulded plastics pots **103** which are lipped to enable them to engage the periphery of appropriately sized apertures **101, 102** in the turntable disc **100** which is rotatable about a vertical axis. The two annular rows **101, 102** of apertures are arranged with the individual apertures of one row **101** alternating in the circumferential sense with individual apertures of the other row **102.** In other words, no one aperture has its centre line on the same radial line as another. Radially inwardly of each pot-receiving aperture, there is a radially extending line of eight holes **105** (FIG. **2**) of smaller diameter than the pot-receiving apertures. These smaller apertures **105** serve as a part of the control system of the apparatus, and each denotes a different degree of dilution required for the portion of the sample (or next specimen) to be deposited in the incubation train. It will be apparent that the radial rows of control apertures **105** also form eight annular rows and a micro-switch (not shown) is associated with and lies below each circular row so that a peg **104** inserted in one of the apertures **105** trips a micro-switch appropriate to the final degree of dilution (or non-dilution) selected and this in turn controls the operation of the transfer means **112** and pump hereinafter described in greater detail. The pegs **104** are held in place by a circular plate **106** (FIG. **1**) and the disc **100** as a whole is readily removable from the apparatus.

It will be noted that four of the receptacle-receiving apertures **101, 102** are omitted, one from the outer row and three from the inner row, and the corresponding control holes are also omitted. This facilitates starting and stopping a cycle of operation.

Inwardly of the holes **105,** two further, inner, rings of dilution-control holes **105'** are present for providing, for example, a 2:1 or 5:1 dilution of the sample and again pegs **104** can be inserted therein to provide the required dilution rate in co-operation with appropriate micro-switches (not shown). A horizontally extending flange **106A** (broken lines) upon which the disc **100** is mounted by keying also actuates by means of an annular row of recesses **107,** two indexing micro-switches **107'**. These position-control micro-switches **107'** serve to control the indexing movements of the disc **100** through positions in which pots of the outer row **102** are available for sample delivery and on completion of pots of this row a switch **107''** engages a recess **106B** and thus causes the flange to be indexed initially through one half of the pitch of the recesses **107** so that the other one of the switches **107'** becomes operative. The flange is then indexed as before until the recess **106B** which actuates the switch **107''** again actuates the switch to stop the apparatus when all the specimens have been dealt with.

The switch **107** also initiates a change in operation of the delivery and dilution arm, in that the transverse movement is extended to cover the inner row. The turntable disc **100** is driven intermittently by an electric motor (not shown) and is stopped exactly in each indexed position by a brake (likewise not shown) under control of the indexing switches **107'**. Alternatively if a synchronous motor is used, the brake can be omitted.

Details of the control system have been omitted from the general description but are illustrated by FIG. **14,** however, at this stage attention is drawn to the timers arranged conveniently in a bank T and the relays in a bank R. A power supply input is indicated at S and a control panel C lies between the timer bank T and the turntable **100.** A vacuum gauge V indicates the vacuum applied to the filter process in the analysis counter.

The turntable **100** lies adjacent the delivery means and the transfer means **109, 112.** The band **111** is vacuum-formed to provide the continuous series of transverse rows of depressions **110,** seven in each row. To reduce interruption in the operation of the machine, it is clearly desirable to have a supply of dilution containers in the band which will last for at least one day of continuous operation.

For a reason which will appear hereinafter a probe for delivering the original sample and successively diluted samples to the dilution containers is in the form of a curved hypodermic type needle and because of the curvature there is a tendency for the liquid delivered to take on an undesirable component of motion which results in the liquid spilling over the rim of the container which is clearly inadmissible. To prevent this each dilution container (FIG. **3**) is formed with a flat bottom **110A** and a frustoconical side wall **110B.** The side wall **110B** extends at an angle of 92½° to the plane of the bottom **110A.** Although increased manufacturing difficulty may result, even greater certainty that spillage

will be avoided can be achieved by making the side wall diverge downwardly (not illustrated).

At the region where dilutions are made up, it is essential that the band **111** should be kept flat and to achieve this two transverse bars **111A** and **111B** are mounted on the framework of the apparatus. It is possible to roll the band **111** and the resultant roll is conveniently disposed below the framework of the apparatus.

Once a diluted or undiluted sample has been transferred from the corresponding dilution container, the remaining samples are no longer required and as shown in FIGS. **1** and **3** a row of seven probes **108** preferably terminated by short flexible tubes, is controlled to dip into respective containers downstream of the transfer means **112** and draw off to waste the unwanted material. This disposal step is timed by appropriate switches to occur immediately after the band **111** has been indexed from the transfer position and before the band has moved to a tilted position. FIG. **3** shows, in outline, a band-indexing motor **113** which drives the band **111** through a pulley **114** having a plurality of spaced pockets or recesses **114A** into which outer surfaces of the containers **110** of one longitudinally extending row thereof engage. Each probe **108** is of approximately U-shape and is pivoted at **115** for movement between the full line and chain line positions. The pivot **115** is oscillated by a bell-crank lever **116** driven by an eccentric **117** itself driven by an electric motor **118.** The electric motor **118** is controlled by a micro-switch (not shown) positioned to sense the arrival of a recess **114A** in the band drive pulley **114.** This reduces the risk of poor alignment which might possibly arise with poor positional tolerances in the band.

The delivery means **109** includes a horizontally extending tubular arm **120** mounted in a bearing block **121** adjacent the band **111** and this arm is capable of transverse movement across the band **111** to overhang with a radial finger or other extension **122** together with its pick-up probe **122'** one or other of the rows of original specimen pots **103.** When a proportion or the whole of the specimen has been picked up through the probe **122'** by suction action of a combined peristaltic and bellows pump (see FIGS. **10** and **11**) fron one or other of the rows of original samples on the disc, the arm **120** is indexed transversely across the band **111,** the first container encountered receiving the neat sample (or a proportion thereof) (forced out by a power stroke of the pump). The probe **122** has the form of a hollow arcuate needle with its centre of curvature coincident with the axis of rotation of the arm.

As hereinbefore described the incubation containers **131** have been so shaped as to reduce as far as possible the risk that delivered liquid will shoot out of the container particularly if the probe needle has a conventional hypodermic shaped end portion. By modifying the end portion, for example by forming a pair or even two pairs of longitudinal slots and then closing the resultant tongues together at the tip, but not along the lengths of the slots, sideways delivery of the liquid will further reduce the tendency for liquid to shoot out of the containers. Other forms of side delivery probe needles can be used, but must retain a piercing capability as will be appreciated hereinafter. A flexible tube **122''** (FIG. **1**) connects the probe with the pump. According to the desired degree of dilution beyond the first which is selected to be 2:1 or 5:1 or any other desired ratio, the arm **120** continues to index across the dilution band, withdrawing an aliquot from each container after a delay for mixing, and adding diluent to the withdrawn proportion of the sample so that the dilution increases progressively in predetermined steps to the end of the row of recesses **110.**

The arm **120** is driven intermittently by a worm **123** (only part shown) in co-operation with a cam follower **124** and a plurality of fixed notches **125** which constitute a "linear" cam **126** and impart a pivotal motion to the arm at each successive dilution depression. The cam **126** exerts a control function over most of its length and a rod (not shown) which engages in a wide slot in the lower surface portion of the arm **120** and is driven by an eccentric of an electric motor which does not in any way hinder the action of the cam. The latter is energized through the micro-switches **127.** The slot narrows at the position along its length which corresponds to the end of the dilution steps where the probe is cleaned by a device described hereinafter in detail with reference to FIG. **5.** This narrowing of the slot has the effect of enabling the rod to force the probe through absorbent paper tapes of the cleaning device, the cam action being insufficient for this purpose. At each notch **125** one of the micro-switches **127** is engaged by the cam follower or a separate actuator and when all the required dilutions have been made, the arm **120** is retracted to an initial or starting position with the probe clear of the band **111.** The follower **124** is, of course, spring biased towards the cam and the micro-switches are electrically connected to the worm drive motor (not shown) (or a direct coupled synchronous motor with a reduction gear) so that the advance is intermittently interrupted. Resumption of the longitudinal motion is controlled sequentially by a timer.

The transfer means **112** includes an arm **128** of generally similar construction to arm **120** and serves to remove by suction action, generated by a combined peristaltic and bellows pump, a proportion of the selected sample of preset dilution and transfer this sample to one of the incubation containers **131.** This transfer takes place at two dilution container pitches downstream of the first. Because this arm **128** operates only between two predetermined points, the notched linear cam of the first arm is not suitable and the required pivotal motion at the take-up and discharge stations is effected by a small electric motor **128''** controlled by micro-switches of the turntable **100** and cooperating with a narrow slot **128A** in the lower surface portion of the arm through a crank mechanism and rod (not shown). The arm **128** is driven longitudinally by a worm **129,** which is in turn driven by a worm **129,** which is in turn driven by a worm wheel **136** keyed to the shaft **137** of a reversible electric motor **138.** Again, it would be possible to drive the worm by a direct-coupled synchronous electric motor and reduction gear. The micro-switches which control the motor **138** are operated by the corresponding peg **104** which is set to the required dilution. The arm **128** carries a probe **139** and a flexible tube **139'** (FIG. **1**) for delivery of wash liquid to wash the interior of the tube after delivery of the selected sample. The probe **139** is arcuate about the axis of its carrying finger **139''.**

To effect transfer of the undiluted samples, diluted samples and the supply and removal of wash liquid it is convenient to use peristaltic pumps since such pumps overcome sealing and, to a large extent, contamination problems. The delivery of a sample from the turntable

100 is effected through a pipe connected to a peristaltic pump denoted generally by reference P combined with a bellows pump 161 and will be further described hereinafter.

The selected sample is transferred by the arm 128 to one of the containers 131 FIG. 6, in which the incubation is to be carried out, here termed "an incubation container." These incubation containers are vacuum-formed from sheet plastics material. Each container 131 has a hemi-spherical base, surmounted by a frusto-conical wall. The exact form of the incubation containers is otherwise not critical because they will normally contain reagent and the risk of transferred liquid shooting out is small because of the energy absorption provided. The containers are arranged as a single row and are interconnected by the continuous web 130 in such a manner that the web can flex in a horizontal plane whilst the containers are disposed with their longitudinal axes vertical. The train of incubation containers also includes laterally extending flanges 132 which serve to connect each container 131 with the web. EAch flange is chamfered at 133 to enable the web to flex between individual containers through a substantial angle, say 45° at a bend in a horizontal plane. The manner in which the web can be made to change direction is illustrated in FIG. 6 which shows a pulley 134 having a plurality of equally spaced pips 135 which engage corresponding holes in the web 130. The web is normally made up with batches of 300 incubation containers and for convenience is made with a short leader (i.e., with no containers) and a long tail. The latter includes ten containers which are not loaded with the reagent that has to be refrigerated. In the web alongside the first of these unloaded containers an aperture is provided for a purpose to be described hereinafter.

After any given transfer operation has been completed, to avoid contamination of the succeeding samples, the outsides of those parts of the arcuate probe 122 and the arcuate probe 139 which dip into the samples are wiped by two tapes 141, 142 of absorbent material such as filter or blotting paper. The tapes 141, 142 as shown in FIG. 5 are unwound from two spools 143, 144 and pass through guides 145 from which they pass to respective spaced horizontal paths. Two guides 146 intermediate the length of the horizontal paths are spaced apart along these horizontal paths by a distance corresponding to the spacing of the probes 122 and 139 and each guide 146 has apertures 147 for the accommodation of the respective probes 122 and 139. The tapes 141, 142 are indexed by a synchronous motor every minute synchronously with movements of the delivery and transfer means. The probes are so spaced and the tapes 141, 142 are so indexed that the probe 122 passes through the tapes at successive spaced positions whilst the probe 139 passes through the tapes at spaced positions intermediate the spaced perforations made by the probe 122. The purpose of two tapes is to ensure thorough wiping of the exterior surfaces of the probes by the upper tape 141 and the removal of any remaining drips at the ends of the probes by the lower tape 142. The tapes pass to a waste bin (not shown) after use.

Isotopically labelled reagent is added to the refrigerated reagent already in the incubation chambers simultaneously with transfer of the selected diluted sample and is delivered thereto by a peristaltic pump of very small capacity to be described hereinafter.

In order to avoid undue evaporation of dilution samples as they are passed through the incubator, it is necessary that the incubator containers 131 should be covered. A convenient device 170 is illustrated in FIG. 7 and carries a tape 171 with a plurality of discs of self-adhesively coated paper or metal foil 172 and these are dispensed through a dispensing opening 173 immediately adjacent the station at which the selected diluted sample is transferred and thus adjacent the inlet to the incubator 150 and the empty tape 171' is wound back on a spool driven by a step-by-step geared-down electric motor 174. The tape 171 itself does not leave the dispenser 170 but the action of moving through a bend of 180° around a plate 174' causes detachment of the individual discs 172 and by correct adjustment it can be ensured that successive discs are centered over the top of and become adhesively attached to each incumbation container 130. These discs prevent spillage at all stages of incubation. The drive motor 174 for the wind-up spool is energised by a timer synchronized with the indexing movement of the incubation container web but is deenergized by a micro-switch 174A having a sensor 174B in the form of a light wire which is effective to operate the switch as an incubation container is indexed forward. It also serves to locate the disc 172 on the corresponding container. If necessary, a sponge wiper (not shown) can be arranged downstream of the micro-switch to press the self-adhesive discs firmly on to the containers.

On completion of the incubation stage for removal of the incubated sample, the disc 172 can be penetrated by a sample removal probe, hereinafter described, without any risk that wash liquid subsequently passed into the incubation container can spill over the top thereof.

At the entry to the incubator provision is made for driving a first one of the pulleys 134 (see FIG. 7) and for imparting to the incubation containers a vibratory motion. The drive pulley 134 is secured to a shaft 180 on which is also mounted a concentric hollow shaft carrying a spaced vibration-producing wheel 181. The wheel 181 has two spaced peripheral flanges 182 which accommodate in the groove thus formed a continuous spiral spring 183 preferably plastics covered. A separate continuously operable drive is provided for the wheel 181, the details of which are conventional and hence not illustrated. The wheel 181 is so disposed that it acts on the outside of the incubation containers and agitates the contents thereof.

The incubator 150 will now be described in more detail with reference to FIG. 8 of the accompanying drawings. As will be apparent from FIG. 1 the web 130 extends in zig-zag formation throughout the incubator and three of the pulleys 134' are mounted on a common plate which is spring biased to tension the web 130. To provide for adjustment of the capacity of the incubator, the pulleys and the plate together with spring biasing means can be removed bodily and relocated at a number of different positions along the incubator length. The purpose of this spring biasing is to take up any tolerance in the web and ensure synchronism of movement of the containers attached to the web and thus to ensure identification of the samples at inlet and outlet of the incubator.

The temperature in the incubator is controlled by a known feed-back temperature controller (not shown), a heater 151 being provided in a chamber 152 below

the incubation chamber **153** which is supplied with a flow of air by means of a tangential flow fan **154** which extends substantially across the breadth of the incubator. The chamber **152** acts as a mixing chamber of the air and thus the air flowing to the incubation containers has an even temperature across the profile of the flow. There is constant recirculation of air from the chamber **153** through the fan **154** to the chamber **152.** Although basically a recirculatory system, if there are any parts of the chamber **153** which does not achieve the desired temperature because of inadequate air flow, bleed holes can be provided in the adjacent chamber wall thus deflecting air flow to that part. The last of the pulleys **134''** is driven intermittently through a geared motor (not shown) synchronised with the delivery of the diluted sample at the inlet of the incubator. Immediately upstream of this last pulley **134''** is the incubated-sample removal device **160** which not only removes the incubated smaple itself, but also acts to wash out the container thorougly to avoid loss of any of the active materials in the sample. The presence of the added diluent or wash liquid at this stage is of no consequence, since it does not affect the quantity of solid protein or other material to be determined.

The band **111** is indexed through the incubator by only two of the pulleys **134,** the first and the last. Both are driven through synchronous motors (not shown) connected in the same circuit and energized by a common timer one every minute. Both motors are normally de-energized by a micro-switch (not shown) positioned for actuation by the pips **135** of the last pulley **134''**. It is important that these indexing movements should be synchronized because the incubation period would be slightly extended or reduced in the event that one more or one less incubation container were to lie within the incubator. Moreover, any identification system would be disturbed. To overcome this difficulty a further micro-switch is placed for actuation by the pips **135** and with its actuating arm disposed one half of the pip spacing downstream of the first-mentioned micro-switch. In the event that the signal for stopping the motors is given between the time a given pip **135** leaves the first micro-switch and reaches the second micro-switch, the motors are stopped by the arrival of the next pip at the contact of the first micro-switch. If, however, the signal to stop is received after a given pip has passed the intermediate switch, then the intermediate switch circuitry allow both pulleys to index to a further pip (i.e., the third) of each pulley. This will mean that one container is not used, but since the sequence is preserved and also the incubation time, this will not be of any consequence.

The incubated-sample removal device **160** (FIGS. **9A, 9B** and **9C**) includes a probe **162** for removing the sample from successive incubation containers and a diluent delivery tube **163** the end of which may be, but is not essentially arranged to deliver diluent tangentially to the surface of the container. Both the probe **162** and the delivery tube **163** are mounted for movement into and out of the incubation containers **131** and when arranged to remove liquid therefrom, the probe extends substantially to the bottom of the container whilst the latter is supported on a platform or bracket (not shown). In this configuration a head **192** carrying the probe **162** and tube **163** engages the top of the incubation container in question through the intermediary of a seal **193.** Air under slight super-atmospheric pressure is delivered to the container through an inlet **194** and this action forces the sample out through the probe **162.** Wash liquid is then supplied through the tube **163** and forced out by re-application of the pressurized air to the container. A total of six wash and delivery cycles is carried out before the incubation web **130** is indexed forward and delivered to a waste container (not shown). On completion of the removal and washing cycle the head **192** is, of course, raised to enable the containers to be indexed on one step.

The peristaltic pump for supplying the device **160** comprises basically a resilient air pipe **195** arranged in two arcuate portions **195', 195''**, a resilient wash liquid pipe **196** arranged as a signle arcuate portion and rollers **197** (in the form of ball bearings), which cooperate with the air pipe and with the wash liquid pipe **196.** The air pipe **195** is open to atmosphere at one end **198** and communicates, through an extension thereof or through a separate pipe with a passage **194A** in the head **192** leading to the inlet **194** via a bellows (FIG. **9B**). The wash liquid pipe **196** communicates with a source of wash liquid and with the liquid discharge tube **163.** The air pipe **195** is subjected to the action of the roller over a first arcuate portion **195'** and over a second arcuate portion **195''**. The liquid pipe **196** extends over an arcuate length of about 90°. To prevent reverse flow of liquid a rubber sleeve type valve **200** or other stop means acts on the pipe **196** between the pump and the head **192,** the loading being such that operation of the pump produces sufficient pressure to overcome the spring loading.

It will be appreciated that to perform the initial displacement of the incubated sample and to perform six wash cycles, pressurized air has to be introduced seven times whereas wash liquid has to be added only six times. It follows that the pump cannot complete only six and a half cycles since otherwise commencement of the next removal and washing step will be out of phase. To overcome this difficulty a bellows **202** is provided which supplies the initial flow of pressurized air to the container and is actuated by the same mechanism as the removal device as a whole, such as a motor driven crank mechanism with a cam plate **192A** mounted on the crank plate **192B.** A cam follower **192C** is connected to a base member **192D** of the bellows and thus causes reciprocation of the bellows folds. Externally of the bellows is a knurled cylindrical casing **192E** which has an annular flange at one end engaging a peripheral portion of the base **192F.** The other end of the casing **192E** has an internal screw thread which engages a complementary thread on a circular end plate **192G.** The latter carries internally of the bellows an elongate hollow guide member **192H** and a complementary member **192J** rigid with the base member **192D** which is slidable therein. The end plate **192G** carries one end portion of the pipe. As will be apparent rotation of the knurled casing varies the effective stroke of the bellows. This bellows **202** is shown in FIG. **9B** and includes provision for adjustment to accommodate requirements of different quantities of incubated liquid in the containers **131.** An air pipe **194B** leads from the peristaltic pump and a further pipe **194C** provides communication between the bellows and the head **192.**

The liquid/solids mixture is discharged from the device **160** on to a continuous filter material belt (not shown), preferably of filter paper or glass fibre, and the solids content of each sample is successively subjected

to analysis by a radiation counter. This latter step is conventional in radioimmunoassay and will not be further described. The filter bed comprises a glass fibre web which is drawn progressively over a perforated drum at the position of deposit of the samples, the liquid being drawn through the perforations with the aid of a partial vacuum (and indicated by the gauge G adjacent the control panel) maintained within the drum.

Immediately prior to the deposition of each incubated sample on to the filter tape, the latter is pre-soaked to avoid loss of vacuum as the tape passes over the vacuum drum. The pump to supply this pre-soak fluid is synchronised with the motor for indexing the tape.

The refrigerated chamber **140** contains a large number of the incubation containers **130** each containing one of the reagents. The continuous web **131** carrying the containers passes on leaving the refrigerator space proper through a tunnel **140'** which leads substantially to the point at which the analysis sample is added. This tunnel **140'** ensures that the temperature of the reagent is kept satisfactorily low so that no deterioration can occur prior to the adding of the selected diluted samples. The chamber **140** is maintained at a temperature in the range −15° C to −5° C. To ensure continued refrigerated conditions to the point at which the sample and second reagent are deposited in the incubation containers, a passage (not shown) below the tunnel provides for recirculation of cold air from the chamber **140.** Circulation is in such direction that cold air leaves through the tunnel and returns through the passage.

The various transfer devices all make use of peristaltic pumps since these pumps are basically reliable, give rise to no contamination problems, there is substantial absence of risk of stale reagent or other liquid remaining in any dead space and the pumps are operable discretely. The particular requirements of the analysis apparatus in accordance with the invention necessitate substantial changes to a conventional peristaltic pump.

The peristaltic pump illustrated in FIGS. **10** and **11** includes a fluid inlet pipe **164** which is connected to a resilient tube **165** of generally U-shape the other end of which is connected to a rigid pipe **165'**. Pumping action within the tube is effected by a pair of conventional ball bearings **166,** the outer races of which roll along the inner periphery of the circular part of the tube **165** whilst the bearings as a whole are rotated by a plate **165''**. A part of the pipe **165'** opens into a small chamber **166'** in a base plate **166''** of the pump and this chamber is closed by a diaphragm **167** across the mouth of a bellows pump **167'**. The latter is actuated by a rod **167''** carrying a cam follower **168** which is subjected to the action of an eccentric **168'**. The eccentric **168'** is so timed that just at tne end of a delivery stroke of the peristaltic pump a suck-back action is caused by the bellows but it will be appreciated that the bellows is not contaminated by any liquid used in the analysis because of the diaphragm **167** and can conveniently be filled with a coloured liquid so that in event of failure of bellows leakage can at once be detected. FIG. **10** shows the inlet to and outlet from the chamber **166'** purely diagrammatically. In practice the chamber is circular and with the longitudinal axis of the chamber horizontal the inlet lies at the bottom of the chamber and joins the periphery. A pump such as that illustrated in FIGS. **10** and **11** delivers liquid via an outlet **169** to the probe **122'** and is programmed by a timer (not shown) for sequential operation to deliver appropriate quantities of diluent liquid through the probe.

A modification of the pump illustrated in FIGS. **10** and **11** is illustrated in FIG. **12.** Similar parts have been given the same reference numerals. In this modification a particularly accurate delivery of reagent or other liquid can be achieved. The bellows of FIGS. **10** and **11** may or may not be incorporated. It was found necessary to make this modification for certain purposes to take into account the loss in theoretical delivery due to the presence of the rollers on approximately 16 millimetres of tube length for each roller. The difficulty of producing an exact delivery each time of a very small quantity of liquid for example 0.05ml. (this can be very important where continuous sampling is carried out with costly reagents) is met by the introduction of a third roller **190** the radial position of which in relation to the peristaltic tube can be adjusted but not sufficiently to produce a pinch effect. This third roller **190** runs in contact with the inner periphery of the peristaltic tube and as will be appreciated adjustment of its radial position enables the quantity delivered to be exactly controlled. A spool **191** serves with the aid of a non-contamination lubricant to maintain the tube **165** in correct alignment. A pump such as that described in FIGS. **10, 11** and **12** can be driven by a small synchronous motor with a reduction gear box and for every cycle the motor can be stopped accurately at a precise position by a micro-switch.

Although the pumps used for the various functions hereinbefore described are of the same general form some discussion of the actual pump units used will now be given. The pump unit used to draw up the required portion of the original specimen and to deposit in the first dilution chamber is, in substance as described with reference to FIGS. **10** and **11.** To bias the cam follower of the bellows on to the eccentric an external spiral spring is used since the inherent resilience of the bellows is insufficient to provide the necessary bias. This is preferable to an internal spring since the loading on the bearings of the pump motor is reduced.

The pump which co-operates with the transfer means **112** incorporates the device for adjusting the throw of the eccentric as hereinbefore described and further incorporates switch actuators **210** and **211** as illustrated in FIGS. **13A, 13B** and **13C.** The actuator **210** is integral with a sheet metal ring **212** which also carries a projection **213** on the face thereof opposite the actuator. The projection supports one end of a screw-threaded member **214** of arcuate form and that portion of the ring below and radially outwardly of the member is cut-away. The actuator **211** is integral with a sheet metal ring **215** which also carries a projection **216** on the face thereof opposite the actuator. The projection **216** when the rings are assembled together extends through the cut-away of the ring **212** and an aperture therein is engaged by the arcuate screwed member **214.** To lock and adjust the relative angular positions of the actuators **210, 211** two nuts are arranged on the member **214** so as to straddle the projection **216.** A third ring actuator (not shown) is also provided for this pump and each of the actuators co-operates with a corresponding microswitch. Although this third actuator can be adjusted with respect to actuators **210** and **211** this is only possible by dismantling the actuator assembly. The actuators **210** and **211** enable the amount of diluted sample delivered to the incubation containers

to be adjusted and this amount is always less than the amount drawn up from the dilution containers. After delivery of the predetermined amount of sample the pump is cycled with wash liquid a number of times when the probe is above the filter tapes, the remaining sample thus being thoroughly washed out.

Finally, the pump for dispensing the second reagent is basically as described with reference to FIG. 12. It will be noted that no bellows is incorporated in this pump and that it operates on a half revolution cycle, that is exactly 0.05ml of reagent is dispensed for each half revolution. This is achieved by the provision of a second radially adjustable roller, which need not be diametrically opposite the roller illustrated. By careful adjustment of both rollers an exact balance of the half revolution deliveries can be achieved. It is important that the needle which delivers the reagent should be such that the resistance in the delivery line should be as low as possible, without however being of large cross-section since any large drip formed at the end of delivery would tend to creep up the outisde of the needle, although this can be minimized by keeping the needle vertical. In any event the action of a peristaltic pump is such that the delivery stroke is immediately followed by a slight suck-back and providing that the needle section is not over large any drip will be rapidly withdrawn.

The spool of the pump shown in FIG. 10 has a periphery of concave semi-circular section. As an alternative the annular section tube can be replaced by a tube of P section and the leg of the P can be positively secured.

In order to adjust the amount of fluid sucked up by the bellows part of the combined pump it is possible to make an adjustment of the throw of the driving eccentric. A block carrying the eccentric roller is disposed in an appropriate central cavity in a disc mounted on the side of the peristaltic pump casing and the block is constrained by a pair of screws engaged in tapped radial bores in the disc to maintain its desired position. The block and hence the eccentric throw can readily be adjusted by rotating the screws in such a manner that they move bodily within the disc in the same linear direction.

As hereinbefore mentioned the incubation web **130**, when prepared for an analysis sequence, has its containers pre-filled with a reagent which has to be kept under refrigeration conditions until immediately prior to the addition of the other reagent and the sample. About ten of these containers at the terminal portion are kept empty and in the web adjacent the first of these containers there is provided an aperture which is engaged by a micro-switch immediately adjacent the sample removal device. The micro-switch remains dormant throughout the analysis sequence and is so connected that, when actuated, in place of the wash liquid used for washing out each container, the sample removal device is supplied with distilled water so th t all the passages are thoroughly cleaned prior to shutdown. The micro-switch also operates a timer so that on completion of five or six distilled water cycles the apparatus is shut down.

Beyond the last container there is a tail of a length sufficeint to extend through the incubator and this tail remains in the incubator until the next sequence is initiated. The initial portion of the next sequence makes use of the remaining four or five empty containers to prime the sample removal device ready for washing in the normal manner.

In each of the peristaltic pumps employed in the apparatus the tubing is expected to have a long period of useful life, but nevertheless replacement is necessary periodically. This is achieved by splitting the pump casing into a part which includes the cavity constraining the tube to arcuate shape and a part which includes the inlet and outlet connections. Externally the inlet connections may be made by any suitable connectors, but internally the connections are made by tapered hollow spigots which engage in the free ends of the tube. Engagement by the spigots progressively distends each tube end portion and forces it against a screw thread cut in the bore leading to the internal cavity. On dismantling the two parts the tube at once becomes accessible and manual rotation of the pinch rollers at once renders one end portion of the tube available to be grasped by the operator.

FIG. 14 illustrates the electrical circuits which provide for the manual and automatic operation of the analysis apparatus. The items illustrated are listed on the drawing itself and in conjunction with the following description of the operational sequences the details of the circuit will be readialy apparent to a person skilled in the art.

At commencement of operation it is essential, before switching on, to check that there is a sufficient quantity of each disposable, i.e., reagents, dilution band **111**, incubation web **130**, absorbent paper tapes **141,142** to cover the anticipated work programme. The start button on the control panel is then operated and a check is made that the refrigerator of the refrigeration chamber **140** is on. The filter bed of the analysis counter apparatus is switched on so that a vacuum is applied to the glass fibre filter. The device for dispensing the second reagent (radio-active label) is primed so that the reagent is available at the dispensing probe. A check is made that four lights at the right hand end of the panel i.e., Mains, analysis filter, refrigerator, incubator are on. Other manual functions as necessary, are then carried out including manually drawing incubation container web **130** from refrigeration chamber **140** to the start position. The auto button is then operated and the following sequence is carried out repetitively until all the specimens on the turntable **100** have been completely analysed.

The disc **100** advances to the start position. The machine will go into auto at (T_0 + 2 secs.) on the main timer (M8) after the disc **100** has reached the start position. At this instant all manual buttons are cut-out. Thereafter the apparatus functions automatically until either an empty disc specimen-container receiving aperture **101** or **102** is presented at the dilution position or one of the blank spaces (i.e., those positions where there are no apertures **101, 102**) at the completion of the full disc is presented. At this time an alarm is sounded. The absence of one specimen container will not inhibit the normal working thereafter, but the absence of two successive containers (or blank orifices at the end of the load) will actuate a 6 minute timer (M24). The purpose of this timer (M24) is to provide a reasonable period (Maximum 5 minutes) to change over the disc **100**. If the operation is not carried out within this time, or there are no further specimens to be assayed, then the pre-incubation functions of the machine enter into a shut-down procedure. The incu-

bation and sample transfer functions continue normally. The purposes of shutting down the pre-incubation function are to avoid wastage of disposables, and to allow the pre-incubation functions to be flushed even though there are samples still to be incubated. This simplifies the extension of the completely automatic functioning of the machine.

In the absence of an operator, e.g., after normal working hours, the machine can be left running provided that the pre-incubation functions have been flushed. This considerably extends the capacity of the machine. This is achieved by the provision of approximately **10** empty incubation containers beyond the normal reagent-containing containers and the provision of the hole accurately positioned relative to these empty incubation containers to operate the micro-switch adjacent to the transfer unit.

On operation of this micro-switch by the hole a timer **M10** is started and a solenoid-operated valve changes the fluid supply to the incubated sample removal device **160** from gelatin to a suitable flushing liquid. The incubation train and incubated sample removal functions continue normally, i.e., operating on a 1 minute cycle, but the empty receptacles serve as flushing containers to simplify the automatic flushing of the pump, head and ejection tube of the sample removal device. After a suitable washing period the machine is swithced off automatically by the timer **M10**.

The apparatus in accordance with the invention operates in such a way that the samples are kept discrete with respect to one another and preferably all containers are disposable thus obviating the need for container washout procedures, and eliminating the possibility of cross contamination from one sample to another. Further the apparatus is so arranged that contamination of one sample by another is substantially eliminated.

The use of disposable lightweight containers is advantageous not only because of the avoidance of the extremely thorough cleaning which would otherwise be necessary, but also because of the low cost of the containers, ease of loading and handling.

The preparation of a range of dilutions for each specimen although only one sample is taken for analysis considerably simplifies the operation, construction and programming of the apparatus as will be apparent from the foregoing description.

We claim:

1. In analysis apparatus
- means for successively delivering discrete biological specimens to successive dilution containers at a station at which each specimen is to be diluted,
- means for diluting the samples in the dilution containers at the dilution station to produce from each successive sample a plurality of samples each of different dilution,
- a series of incubation containers,
- means for transferring a sample of selected dilution to one of said incubation containers,
- an incubator for incubating the selected diluted sample in the said incubation container and
- analysis means for analysing the diluted sample.

2. Apparatus according to claim **1**, wherein the analysis means employs radioimmunoassay techniques.

3. Apparatus according to claim **1**, comprising incubated-sample removal means comprising
- a pump operative to remove the incubated sample material from successive said incubation containers, capable of delivering a succession of wash fluid quantities to each said container and successively removing said wash fluid quantities whereby all solids of the sample are removed for analysis by the analysis means.

4. Apparatus according to claim **3**, wherein the incubated sample removal means comprises
- a seal for sealing off each incubation container mouth,
- a probe for delivering air under pressure into the sealed container and
- an outlet through which the incubated sample and successive wash liquid quantities can be delivered to the analysis means.

5. Apparatus according to claim **1**, wherein the analysis apparatus includes a filter tape of glass fibre and a radiation counter.

6. Apparatus according to claim **1**, including circuit means for controlling and effecting operation of the component parts of the apparatus.

7. Apparatus according to claim **1** incorporating
- a plurality of remotely-controlled peristaltic pump units for delivering and transferring quantities of liquid to and from containers of the apparatus, and
- bellows incorporated in at least one said unit operable at the end of each delivery cycle of the unit to produce a suck-back action preventing the formation of drips at a delivery terminal.

8. Apparatus according to claim **7**, comprising a diaphragm sealing off the interior of the bellows from the biological liquid.

9. Apparatus according to claim **8**, wherein the peristaltic pump includes
- means for maintaining the correct alignment of the flexible tube thereof and
- means for adjusting the amount of liquid delivered by each cycle of the pump.

10. Apparatus according to claim **9**, wherein the control means comprises a roller and means for adjusting its degree of contact with the tube at a position intermediate operational pinch rollers of the pump.

11. Apparatus according to claim **7** comprising means for adjusting the timing of the active suction stroke of the bellows relatively to the peristaltic pump stroke.

12. Apparatus according to claim **11**, wherein the adjusting means comprises
- a first ring carrying a first contact,
- a second ring carrying a second contact,
- a screwed arcuate member one end of which is secured to one of the rings and the other end is connected to the other ring,
- a projection on the other ring receiving the other end portion of the arcuate member and
- two nuts threaded on the arcuate member at opposite sides of the projection.

13. Apparatus according to claim **1** wherein said diluting means comprises
- means identifying each said specimen and providing, in the form of a code, the appropriate degree of dilution required in the analysis,
- said transfer means being operable by the code to transfer the contents of a selected one of the dilution containers determined by one of the series of incubation containers.

14. Apparatus according to claim **13**, wherein the transfer means comprises

an arm rotatable about its longitudinal axis and having
a radial extension, and
a probe carried on the radial extension,
said arm being capable under the control of the identifying means of moving the probe into a selected one of the dilution containers and delivering the contents to one of the incubation containers.

15. Apparatus according to claim 14 comprising drive means for the dilution containers including
a wheel having radially extending pockets arranged to be engaged by the outside surfaces of the containers, and further comprising
vibratory means arranged to impart vibration to the containers through an outer one of the longitudinal rows of containers whereby mixing of the diluent is accelerated.

16. Apparatus according to claim 1 comprising refrigerator means for storing the incubation containers together with the reagent used in the analysis.

17. Apparatus according to claim 1, comprising means for wiping surplus material from the transfer means after delivery of the selected diluted sample to the respective incubation container.

18. Apparatus according to claim 17, wherein the surplus material wiping means comprises
a twin layer strip of absorbent paper the layers of which are spaced apart with one layer lying above the other at least in the region of active wiping of the transfer means, and
means for indexing the strip in synchronism with movements of the transfer means.

19. Apparatus according to claim 1, comprising
a disc rotatable about a vertical axis with two rows of peripheral apertures carrying specimen containers, the said disc incorporating inwardly of the peripheral apertures,
sample identifying means in the form of pegs selectively inserted in one or more of a plurality of holes in the disc arranged in radial rows, each row being associated with a corresponding container aperture and substantially aligned with one of the undiluted specimen-container receiving apertures, and
switch means, operable by said pegs, which switch means in turn activate the transfer means.

20. Apparatus according to claim 1, wherein the means for delivering the undiluted specimen to each one of the plurality of dilution containers comprises
a cam-controlled arm,
a probe mounted on the arm and operable to dip into said undiluted specimen container, to pick up the sample, and successively to deliver the specimen into successive diluted-sample containers, and simultaneously to increase progressively the dilution in said successive dilution containers.

21. Apparatus according to claim 1 comprising a web mounting the incubation containers, the mouths of the containers lying in a plane substantially at right angles to the plane of the web.

22. Apparatus according to claim 21, wherein the incubator comprises
means defining a substantially closed chamber,
a plurality of pulleys within the chamber around which the incubation container web is trained, and
means biasing at least one of said pulleys in a direction normal to the rotational axis of the pulley whereby the tension in the web is maintained substantially constant.

23. Apparatus according to claim 21, wherein said incubator comprises
means defining a chamber in which the incubation web is mounted,
means defining a mixing chamber lying below the incubation web chamber,
a tangential flow fan for circulating warm air through the two chambers, and
a heater element in the mixing chamber downstream of the fan outlet.

24. Apparatus according to claim 1, comprising means for placing an adhesive cap over the mouth of each successive filled incubation container whereby the evaporation rate is substantially reduced.

25. Apparatus according to claim 1 comprising a device for flushing a said incubation container of a solids-containing liquid so that substantially no solids deposited by the liquid are left in the container, said device comprising
a head,
a seal carried by the head and capable of sealing off the container at the mouth thereof,
a probe mounted in the head of a length such that the tip thereof can extend substantially to the bottom of the container,
means defining an inlet in the head for delivering gas under pressure to the container, and an inlet for the delivery of wash liquid,
a peristaltic pump for delivery in timed sequence pressurized gas to the gas inlet and wash liquid to the wash liquid inlet, and
means for cycling the gas and liquid through a plurality of pressurization and wash liquid cycles.

26. Apparatus for carrying out continuous discrete analysis of biological specimens using the radioimmunoassay technique, said apparatus comprising
a turntable disc carrying a plurality of undiluted specimen containers,
means on the disc associated with each container for indicating the required degree of dilution of the contents of each container, an undiluted-specimen delivery arm operable to withdraw successively the specimens from the undiluted-specimen containers,
a plastics band formed with a row of dilution containers for receiving the withdrawn specimens,
means for progressively increasing the degree of dilution in the successive dilution containers of the row,
means for indexing the band after a row of containers has been filled with diluted samples of a given specimen,
a series of incubation chambers arranged as a single row and connected to a flexible web,
a diluted sample transfer arm actuable in dependence upon the indicating means to transfer a sample of selected dilution ratio to one of the incubation containers,
an incubator incorporating
means for recirculating continuously a heated air flow and
means for indexing the incubation web through the incubator,
an analysis apparatus,

an incubated sample removal device for removing successive incubated samples to the analysis apparatus,

said analysis apparatus including

a glass fibre tape on which the solids in the incubated samples are retained, and

a radiation counter for counting the radio-active material in said solids,

peristaltic pump units coupled respectively to the specimen delivery arm, the sample transfer arm, and the incubated sample removal device,

electric motors for driving respectively the delivery arm, the transfer arm, and the incubation container web and

timing means for controlling operation of the motors.

* * * * *

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,784,826 Dated January 8, 1974

Inventor(s) KENNETH D. BAGSHAWE and DEREK N. MARCHANT

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 4, line 31, "107" should be --107"--

Signed and sealed this 23rd day of April 1974.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents

FORM PO-1050 (10-69)

USCOMM-DC 60376-P69
★ U.S. GOVERNMENT PRINTING OFFICE : 1969 O—366-334.