United States Patent [19]

Gibbs et al.

[11] **3,854,703**

[45] **Dec. 17, 1974**

[54] **METHOD OF AND APPARATUS FOR PROMOTING A REACTION BETWEEN A LIQUID SPECIMEN AND A LIQUID REAGENT**

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[22] Filed: **Sept. 15, 1972**

[21] Appl. No.: **289,344**

[30] **Foreign Application Priority Data**

Sept. 17, 1971 Great Britain 43575/71
Mar. 30, 1972 Great Britain 15218/72

[52] **U.S. Cl.** **259/11,** 23/259, 259/2, 259/DIG. 24

[51] **Int. Cl.** **B01f 13/02**

[58] **Field of Search** .... 259/1 R, 2, 11, 17, DIG. 17, 259/DIG. 24; 23/253 TP, 259; 261/80; 34/28, 31, 33, 46, 216, 217, 221, DIG. 2

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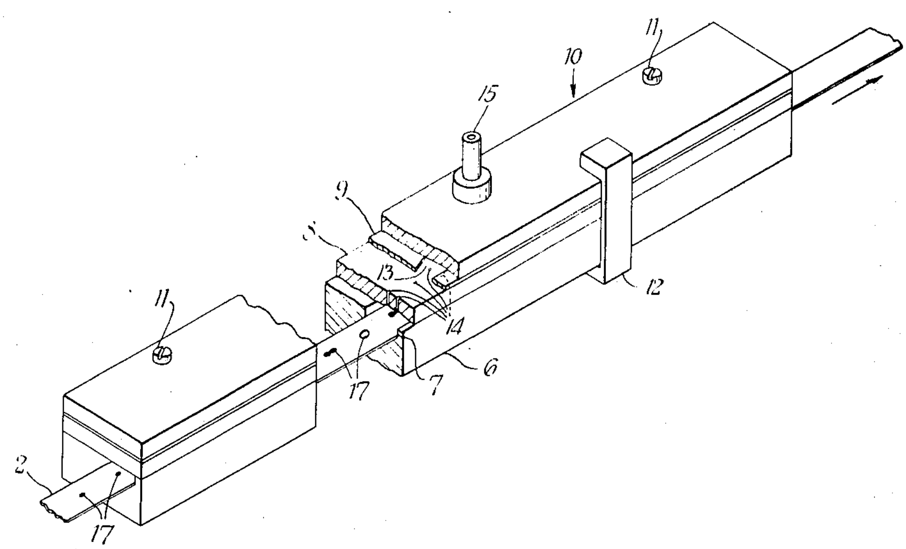
[57] **ABSTRACT**

A reaction between a liquid specimen and a liquid reagent is promoted by applying the liquids to a liquid-impermeable support surface to form a mixture thereon, and the liquid mixture is agitated by directing a jet of gaseous fluid from a supply duct outlet to impinge thereon, and bringing about relative movement between the outlet and the support surface.

10 Claims, 6 Drawing Figures



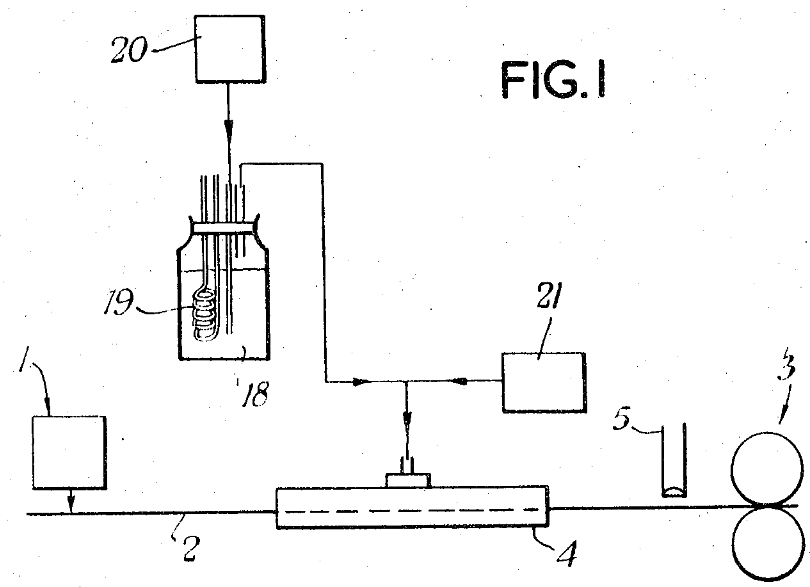
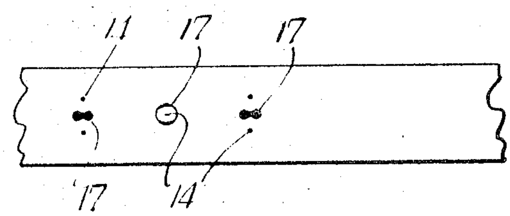


FIG. 1

FIG. 3



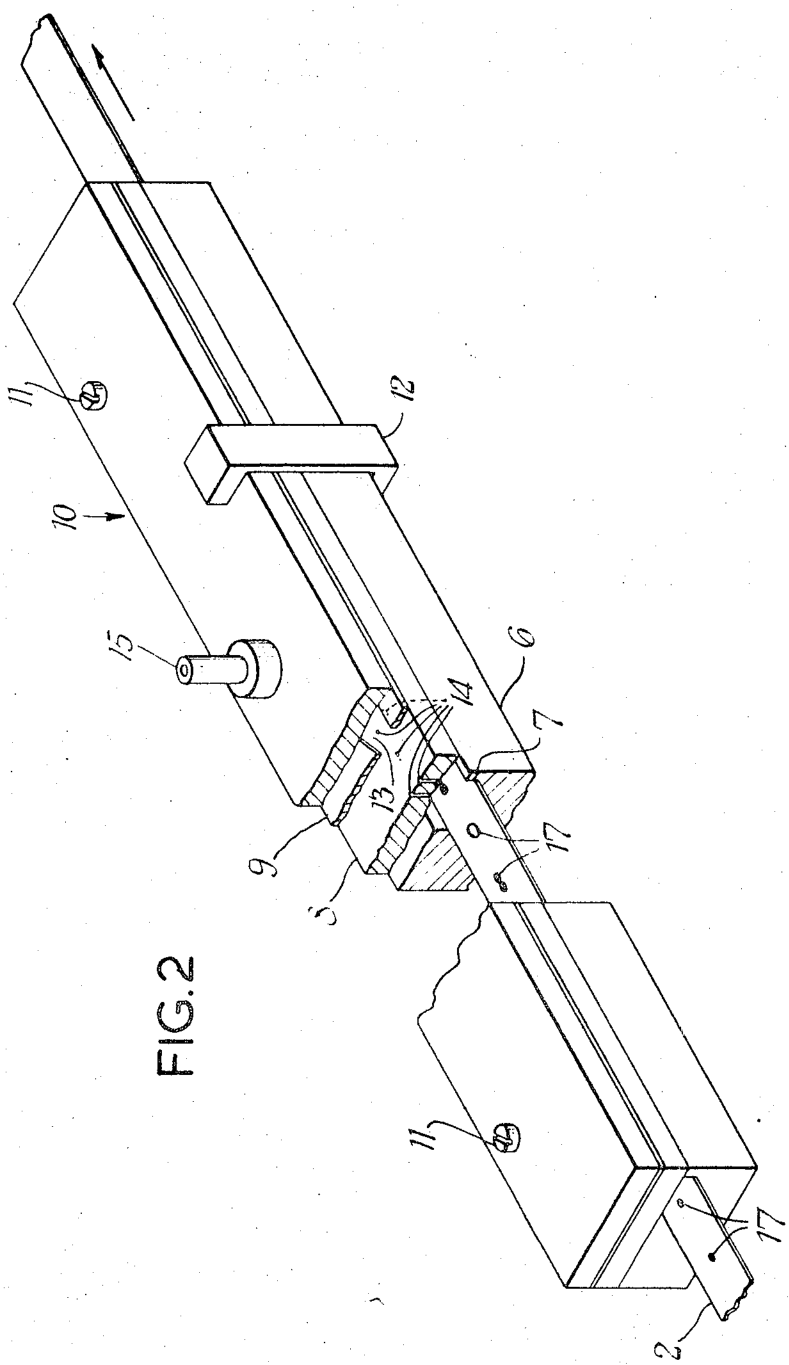


FIG.2

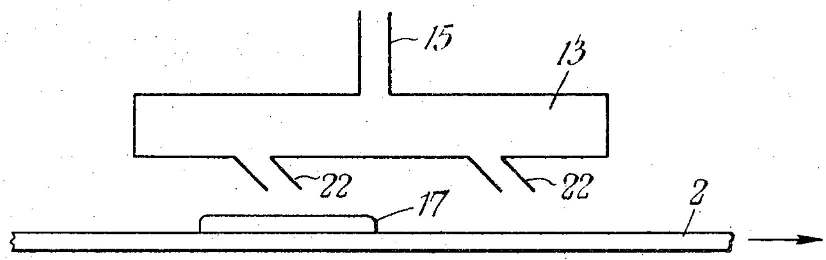


FIG. 4

FIG. 5

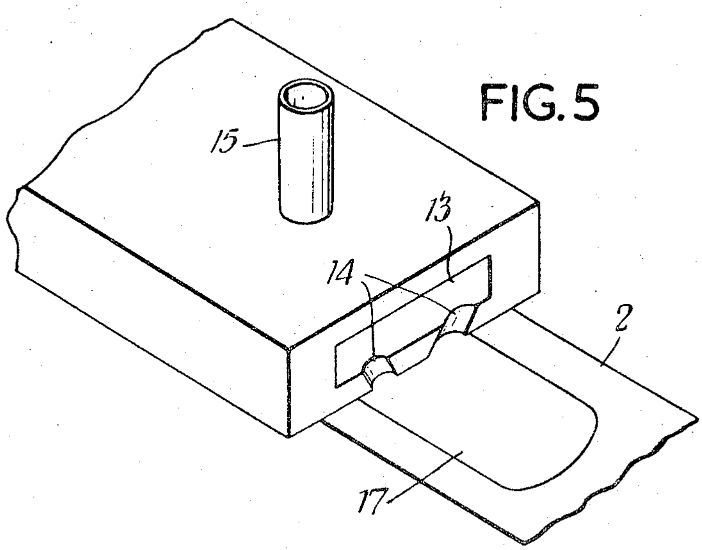
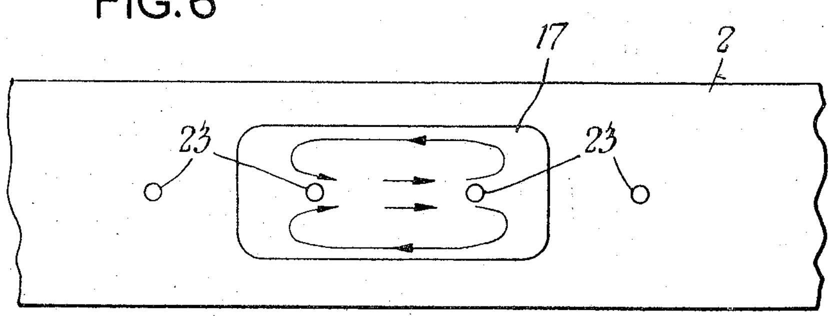


FIG. 6



METHOD OF AND APPARATUS FOR PROMOTING A REACTION BETWEEN A LIQUID SPECIMEN AND A LIQUID REAGENT

This invention relates to methods of and apparatus for promoting a reaction between a liquid specimen and a liquid reagent.

Many tests that are carried out upon samples of specimen material derived from different sources involve agitating the material with a reagent added thereto in order to produce an homogeneous mixture of the reagent and the material. This has been achieved hitherto by stirring the material with a stirring rod. However, it is inconvenient to employ a stirring rod with very small samples, and cross-contamination between samples may be caused if a stirring rod is employed. Accordingly the problem has arisen of how to bring about agitation of very small samples of specimen material, and particularly without causing cross-contamination between samples.

According to a first aspect of the present invention there is provided a method of agitating liquid specimen material distributed for examination over a specimen support surface, wherein a jet of gaseous fluid emerging from a supply duct outlet is caused to be incident upon the liquid material and relative movement is brought about between the support surface and the said supply duct outlet.

According to a second aspect of the present invention there is provided, in combination, a specimen support surface and a supply duct arranged for directing a jet of gaseous fluid from an outlet of the duct to be incident upon liquid specimen material that is distributed for examination over the support surface when it is in use, there being means for bringing about relative movement between the support surface and the said outlet so as to cause agitation of the liquid specimen material.

According to a third aspect of the present invention there is provided a device for agitating liquid specimen material distributed along an upper surface of an elongate specimen support, comprising guide means for determining a path along which the support can be moved in a lengthwise direction thereof through the device, and pneumatic jet-forming means having at least one outlet arranged, adjacent to the said guide means, for directing a jet of gaseous fluid so as to be incident upon the specimen material on the support surface, when the device is in use, thereby to bring about agitation of the specimen material as the specimen support is moved, along the said path, past the or each said outlet.

The gaseous fluid (i.e., gas or vapour) is preferably air.

For a better understanding of the invention, and to show how the same may be carried into effect, reference will now be made, by way of example, to the accompanying drawings in which:

FIG. 1 shows diagrammatically an elevation of apparatus for use in testing specimen materials,

FIG. 2 shows a perspective view, partly cut away, of a device forming part of the FIG. 1 apparatus,

FIG. 3 shows a plan view of a portion of specimen support tape,

FIG. 4 shows diagrammatically a longitudinal sectional view of a first modification of the FIG. 2 device,

FIG. 5 shows a perspective view, cut away, of a second modification of the FIG. 1 device, and

FIG. 6 shows a plan view of a portion of specimen support tape.

The apparatus shown in FIG. 1 is used to perform tests upon specimen materials, for example blood serum, by mixing a sample of each specimen material with reagent and observing the result of the reaction, if any, between the specimen material and the reagent. Thus, the apparatus comprises applicator means **1** whereby a succession of drops of reagent (and possibly also diluent) are applied to the upper surface of a horizontal specimen support tape **2** which is drawn through the apparatus by virtue of its being gripped between two rollers **3** of which one is driven to rotate. The applicator means **1** also dispense a drop of specimen material into each drop of reagent, to provide a succession of pools distributed along the tape and each containing specimen material and reagent. Beyond the applicator means **1** in the direction of tape movement is a pneumatic stirring device **4** whereby each pool of specimen material and reagent is thoroughly agitated to provide an homogeneous mixture. The pneumatic stirring device is shown in more detail in FIG. **2.** During passage of the pools through the pneumatic stirring device the reaction, if any, between the specimen material and the reagent takes place, and the result of the reaction is observed by optical means **5.**

The pneumatic stirring device illustrated in FIG. **2** comprises a tape guide **6** formed with a groove **7** which has a flat bottom and straight sides. A distribution block **8** is positioned above the guide **6** so that it extends completely over the top of the groove **7.** Above the distribution block **8** is a gasket **9** and above that is a manifold top plate **10.** The components **8, 9** and **10** are held together by screws **11** and the guide **6** and the assembly **8/9/10** are held together by a spring clamp **12.**

The block **8,** the gasket **9** and the top plate **10** together define a chamber **13** which extends above the groove **7.** The chamber **13** communicates with the volume bounded by the groove **7** through a plurality of outlets **14.** Air from a supply cylinder **20** (FIG. **1**) can be supplied under pressure to the chamber **13** through an inlet stub **15** provided on the top plate **10,** and it leaves the chamber by way of the outlets **14** forming respective jets directed towards the bottom of the groove. The outlets **14** along the groove are arranged alternately as outletpairs and single outlets.

The device **2** is used to agitate pools **17,** containing specimen material and reagent, distributed along the upper surface of the specimen support tape **2.** To use the device the clamp **12** is removed and the assembly **8/9/10** is lifted from the guide **6** so as to expose the groove **7.** A lead-in portion of the tape is laid in the groove and the assembly **8/9/10** is then clamped in position once more. The leading end of the tape is passed between the rollers **3** for drawing the tape through the groove in the direction of the arrow, and the inlet stub is connected to a supply of compressed air (not shown). The tape is then drawn through the device, along the path defined by the groove in the guide, as the air is supplied to the chamber and issues from it through the outlets **14** forming jets directed onto the upper specimen-bearing surface of the tape. As a pool of the specimen material passes under one of the single outlets that pool tends to be flattened out and pushed aside from the centre of the tape, and as the pool subsequently passes under an outlet-pair the pool is pushed back once more towards the centre of the tape (see FIG. 3). Thus as the tape is drawn through the device the specimen material is agitated. The amount of agitation is controlled by the total number of single outlets and outlet-pairs, while the rate of agitation is controlled by the pitch of the single outlets and outlet-pairs along the groove.

The agitation brought about by the FIG. **2** device is used to promote chemical reactions between the specimen material and the reagent, and in order to prevent excessive drying of the reactants and/or the reaction product the air is humidified by passing the air from the cylinder **20** through a bath **18** (FIG. **1**) of water and mixing it with dry air from a second cylinder **21.** The temperature of the air is also controlled by heating the water of the bath **18** with a thermostatically controlled immersion heater **19.** It may in some circumstances be desired to dry the reaction product, in which case the temperature and humidity of the air are adjusted accordingly. The specimen material may contain insufficient liquid in which case diluents as well as reagents may be added to the specimen material before it reaches the device.

A device in accordance with FIG. **2** has been constructed using Perspex for the components **6, 8** and **10** and butyl rubber for the gasket **9.** A satisfactory amount of agitation was achieved with the device using air supplied to the inlet stub **15** at about 5 p.s.i.

It has been found that instead of using alternate single outlets and outlet-pairs, as described with reference to FIGS. **2** and **3**, it is preferable in order to produce an homogeneous mixture of reagent and specimen material to employ the modification shown diagrammatically in FIG. **4.**

In the case of the FIG. **4** modification, two single outlets provided by jet needles **22** are spaced apart along the groove, without an interposing outlet-pair. The needles **22** are of cylindrical cross-section, and their central axes are inclined to the vertical at 45° but lie in the same vertical plane. The inclined needles are directed forwardly, that is in the direction of tape movement, and air jets provided by the needles induce a vortex motion in the liquid of the pools, thereby producing a thorough mixing of the reacting components. The depth of the groove is such that the clearance between the needles and the free surface of a pool 0.2 mm deep is less than five times the internal diameter of the jet needles. It is found with 10 μl pools containing blood serum and a water-based reagent, and a tape speed of 10 mm/sec., adequate mixing is produced with an air flow to each jet needle of approximately 0.6 l/min. The effectiveness of the jet action is reduced if the clearance between the needles and the pools is increased beyond five needle diameters or if the inclination of the needles to the vertical is reduced below 45°.

Many tests in serology involve agglutination reactions, developed by rocking a mixture of blood serum and a reagent for a period of time. If the mixture is provided in the form of pools on the horizontal tape **2,** the rocking action can be produced by passing the tape under a series of outlet-pairs as shown in FIG. **5.** In the case of FIG. **5** the outlets are provided by respective passageways of cylindrical cross-section. The central axis of each passageway is inclined to the vertical at 30°, and lies in the same vertical plane, perpendicular to the direction of tape movement, as the central axis of the passageway providing the other outlet of the pair. The two jets provided by the outlet-pair converge to form an air curtain above the tape which causes the liquid to be carried towards the back of the pool until it finally passes through the air curtain to flow forward again. The outlet-pairs are spaced apart along the groove by slightly more than the length of the pools in order to allow this pattern of movement to become established. For example, in the case of pools 12 mm long the outlet-pairs are spaced apart along the groove by 15 mm. The outlets are approximately 4 mm above the tape, and for 10 μl pools an air flow through each outlet-pair of approximately 0.6 l/min. is required.

Using the modification shown in FIG. **5** for reactions which require long mixing times and a large number of rocks leads to an undesirably long rocking stage, and in these circumstances it has been found preferable to employ a series of stirring jets as described with reference to FIG. **4,** with a pitch (space between successive jets) less than the length of the pools on the tape. For example, for a 10 μl pool, 12 mm long, the jets are pitched at 8 mm. This creates a steady vortex flow pattern in the pools, as shown in FIG. **6.** In FIG. **6** the positions at which the air jets are incident on the pool **17** and the tape **2** are shown as circles **23.** For 10 μl pools an air flow to each jet of 0.3 l/min. is sufficient. Of course, to increase the amount of mixing the tape speed may also be reduced.

It is not essential for the specimen material to be in discrete pools, as shown, but it could instead be in the form of a continuous trace extending along the tape.

The device shown in FIG. **2,** or as modified in accordance with FIGS. **4** or **5,** may be used in combination with other devices to treat specimen material to prepare it for subsequent microscopic examination, for example in the Vickers Cytological Screening Apparatus.

We claim:

1. A method of promoting a reaction between a liquid specimen and a liquid reagent, comprising the steps of applying the liquid specimen and the liquid reagent to a liquid-impermeable support surface to form a liquid mixture thereon, causing a jet of gaseous fluid to emerge from a supply duct outlet and impinge upon the liquid mixture on the support surface, and bringing about relative movement between the support surface and said supply duct outlet thereby to cause agitation of the liquid mixture.

2. A method as claimed in claim **1,** comprising the further steps of controlling the temperature and controlling the humidity of said gaseous fluid.

3. Apparatus for promoting a reaction between a liquid specimen and a liquid reagent, comprising a liquid-impermeable support surface, first means for applying the liquid specimen to the support surface, second means for applying the liquid reagent to the support surface to form thereon a liquid mixture with the liquid specimen, a source of gaseous fluid, a supply duct having an inlet connected to said source and an outlet arranged to direct a jet of gaseous fluid from said source to impinge upon said liquid mixture on the support surface, and drive means connected to bring about relative movement between the support surface and said outlet thereby to cause agitation of the liquid mixture.

4. Apparatus as claimed in claim **3,** further comprising means for controlling the temperature of said gaseous fluid and means for controlling the humidity of said gaseous fluid.

5. Apparatus as claimed in claim **3,** wherein said support surface is an upper surface of an elongate specimen support and the apparatus further comprises guide means determining a path along which said support is movable in a longitudinal direction thereof through the apparatus.

6. Apparatus as claimed in claim **5,** wherein said outlet is one of a plurality of such outlets all connected by way of the supply duct to said inlet and spaced apart along the path without additional outlets therebetween, each outlet of the plurality defining the end of a cylindrical passageway having a central axis lying in vertical plane parallel to said path and extending from said outlet both downwardly, at **45°** to the vertical, and in said longitudinal direction.

7. Apparatus as claimed in claim **6,** wherein said first and second means are arranged to co-operate to provide on said upper surface as said drive means operate a succession of pools of given depth, distributed along said upper surface and each containing a mixture of liquid specimen and liquid reagent, which are carried on the specimen support from said first and second means and subsequently along said path, and there being between each outlet of the plurality and the upper surface of said support a clearance that is less than the sum of said given depth and five times the internal diameter of said cylindrical passageways.

8. Apparatus as claimed in claim **7,** wherein the number of outlets of the plurality is more than two and the distance between successive outlets is less than the length of said pools.

9. Apparatus as claimed in claim **5,** wherein said outlet is one of a plurality of such outlets which are connected to said inlet and which are distributed along said path, the outlets being arranged alternately singly and in pairs, the two outlets of each pair being spaced apart transversely with respect to said path.

10. Apparatus as claimed in claim **5,** wherein said first and second means are arranged to provide on said upper surface a succession of pools of given length distributed along said upper surface and each containing a liquid specimen and a liquid reagent, and said outlet is one of a plurality of such outlets, said outlets being arranged in pairs and the pairs of outlets being spaced apart along said path by a distance greater than said given length and there being no additional outlets between successive pairs of outlets along the path, each outlet of each pair defining the end of a cylindrical passageway having a central axis which is inclined to the vertical and lies in a vertical plane perpendicular to said path and which crosses the central axis of the cylindrical passageway whose end is defined by the other outlet of the pair below the pair of outlets.

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