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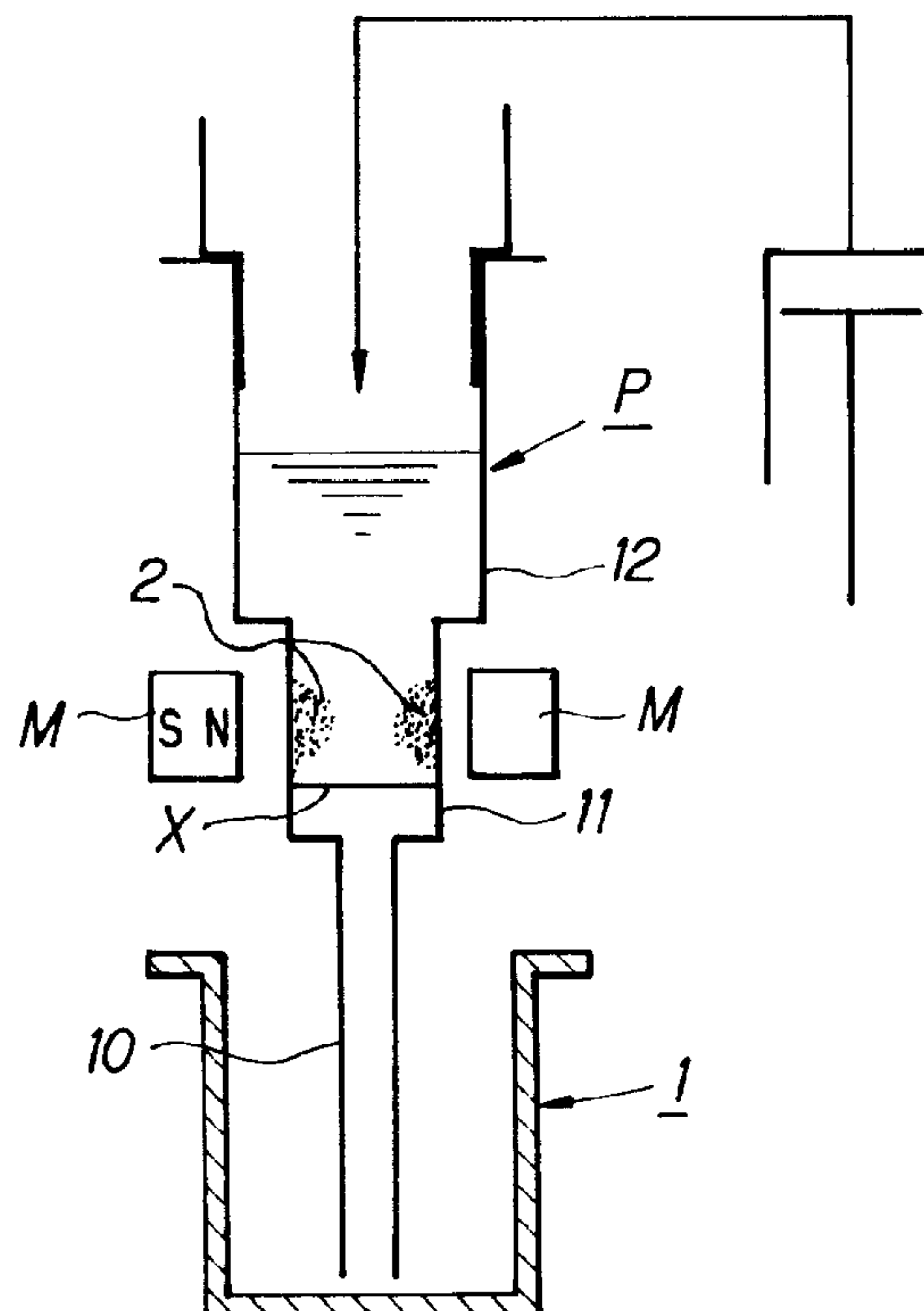
(72) Inventeur/Inventor:
Tajima, Hideji, JP

(73) Propriétaire/Owner:
Precision system Science Co., Ltd, JP

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : METHODE DE CONTROLE PERMETTANT D'ATTIRER ET DE LIBERER DES MATIERES MAGNETIQUES
AU MOYEN D'UNE PIPETTE; TYPES VARIES D'APPAREIL D'INSPECTION CLINIQUE UTILISANT LA METHODE
EN QUESTION

(54) Title: MAGNETIC MATERIAL ATTRACTING/RELEASING CONTROL METHOD MAKING USE OF A PIPETTE
DEVICE AND VARIOUS TYPES OF CLINICAL INSPECTION APPARATUS USING THE METHOD



(57) Abrégé/Abstract:

Disclosed is a method for attracting and releasing a magnetic material by the use of a pipette device for sucking a liquid from or discharging same into a container. A magnet body or bodies are provided in a liquid suction line of the pipette device, and the magnetic material contained in a liquid sucked into the liquid suction line by magnetic force is deposited on an internal surface of the line. The magnetic material is released and discharged together with the liquid from the liquid suction line.



ABSTRACT OF THE DISCLOSURE

Disclosed is a method for attracting and releasing a magnetic material by the use of a pipette device for sucking a liquid from or discharging same into a container. A magnet body or bodies are provided in a liquid suction line of the pipette device, and the magnetic material contained in a liquid sucked into the liquid suction line by magnetic force is deposited on an internal surface of the line. The magnetic material is released and discharged together with the liquid from the liquid suction line.

MAGNETIC MATERIAL ATTRACTING/RELEASING CONTROL
METHOD MAKING USE OF A PIPETTE DEVICE
AND
VARIOUS TYPES OF ANALYZER USING THE METHOD

FIELD OF THE INVENTION

The present invention relates to a novel magnetic material attracting/releasing control method by which a magnetic material may be easily captured or dispersed. The invention also relates to various types of analyzers using
10 the method.

It should be noted that, as defined in this specification, "magnetic material" refers not only to ball-like materials, but also to granular and corpuscular materials. The form is not limited to a sphere and any form is included.

BACKGROND OF THE INVENTION

In recent years, a variety of chemiluminescence methods (CL method) have been developed. These include, for instance, an enzyme immunoassay (EIA) that utilizes an antigen-antibody reaction, a chemiluminescence immunoassay (CLIA) in a narrow sense in which a chemiluminescent compound is used for labeling as a tracer for immunoassays, and a chemiluminescent enzyme immunoassay (CLEIA)
20 which detects enzyme activity with high sensitivity by using a chemiluminescent compound in a detection system.

Such methods have employed a variety of assay techniques including a technique using magnetic particles, each having a surface coated with an antigen or an antibody, a method using latex having a surface coated with an antigen or an antibody, a method using spherical beads each having a surface coated with an

antigen or an antibody, and the so-called tube coating method which uses cells each having an inner wall coated with an antigen or an antibody. Due to varying efficiency in capturing an antigen or an antibody, as well as production and running costs, methods using magnetic bodies, such as magnetic particles or beads, are normally the most advantageous.

Use of magnetic particles in conventional assay methods requires that the magnetic material be cleaned or that a reagent be attached to the magnetic material by gathering suspended or precipitated magnetic material from a reactor such as a specimen reaction container. The magnetic material may need to be re-

10 suspended and gathered several times from the reactor. However, it is extremely difficult to maintain high precision in gathering or agitating the magnetic material in this process; this is one of the reasons why assay methods making use of magnetic materials have not been automated for certain applications.

Figure 9 shows a flow chart describing an immunochemical process utilizing magnetic material as described above. The process involves the following sequence of steps: at first the required quantity of a sample is placed in a container 1 with a first pipette P_1 in step (a); a liquid 2 containing insoluble magnetic material is poured into the container 1 by a second pipette P_2 in step (b). The resulting liquid is agitated by a vibrating agitator in step (c); incubation (at a constant temperature) is

20 conducted in step (d); the magnetic material is gathered together using magnet M and the liquid is discharged in step (e); and a cleaning liquid is then poured into the container using a third pipette P_3 in step (f).

Then in step (g), agitation is carried out by a shaking agitator; in step (h), the magnetic material 2 is gathered together using magnet M with the cleaning liquid discharged; in step (i), a labeling liquid 6 is poured in through a fourth pipette P_4 ; in

step (j), agitation is carried out by a shaking agitator; in step (k), the liquid is incubated at a constant temperature; in step (l), the magnetic material is gathered together using the magnet M with the reaction liquid discharged; in step (m), the cleaning liquid is poured in through a fifth pipette device P₅; in step (n), agitation is carried out by the shaking agitator.

Then, for instance, when the CLEIA method is employed, in step (o), the magnetic material 2 is gathered together using the magnet M with the cleaning liquid discharged; in step (p), a substrate liquid is poured in; in step (q), agitation is carried out by a shaking agitator; and then in step (r), the sample is allowed to sit for a certain period of time; and in step (s), the quantity of light emitted from the reaction system is measured with an optical measuring instrument such as PMT.

On the other hand, when the CLIA method is employed, after step (n) described above, in step (t), a cleaning liquid solution in vessel 1, containing the magnetic material 2, is transferred into a measuring cell by pouring the cleaning liquid through a filter on the measuring cell thus collecting the magnetic material 2 on the filter. Then, in step (u), a hydrogen peroxide (H₂O₂) solution is poured into the magnetic material 2 collected by the filter resulting in transitionally emitted light which is measured by a PMT tightly protected against light coming from outside. Like the CLEIA and EIA methods in which light emission continues for a certain period of time after the substrate liquid is poured in at step (s), the quantity of light generated in the reaction is measured with an optical measurement instrument such as a PMT in step (t).

The above description relates to the conventional type of assay method using a magnetic material. However, as clearly understood from the foregoing, such methods require that the magnetic material be gathered onto the internal wall of a

container and then be homogeneously dispersed into a liquid several times. It is extremely difficult to separate the magnetic material from a liquid, to agitate, and to clean the container at high precision, which is a problem to be solved.

In particular, when separating the magnetic material from a liquid in the conventional type of assay method, a magnet is generally applied to the side wall of a large container. This localized magnetic force requires a long time to attract the magnetic material dispersed in a liquid onto the internal wall of the container. Efficiency in gathering the magnetic material is thus disadvantageously very low.

Also, when gathering magnetic material onto the internal surface of a
10 container and inserting a pipette into a liquid to withdraw the liquid, the magnetic material may be withdrawn together with the liquid, because it is extremely difficult to completely gather together the magnetic material.

Furthermore, when agitating the liquid with the magnetic material dispersed therein, generally vibration is employed to mix with and disperse in the liquid, the magnetic material that has once been adhered to the container while magnetism is suppressed. However, it is difficult to homogeneously disperse the magnetic material in the liquid, and the liquid containing the magnetic material mixed therein sometimes splashes out onto an upper surface of the container, another
20 problem to be solved. As a result, when using vibration to agitate with the conventional technology, the liquid containing the magnetic material which is splashed onto the upper surface of the container must be washed off. Hence, processing becomes more complicated, and if this operation for washing off the liquid is carried out incompletely, the subsequent steps in the process are seriously affected.

Furthermore, when cleaning the magnetic material in the container as described above, materials other than those deposited on the surface of the magnetic

material are removed during processes for separating as well as agitating as described above.

Also, in the conventional assay employing magnetic material, if a reaction process or a treatment process is a very particular one, one is required to design special methods for separation, agitation, and cleaning as well as a control system suited to the specific process. Hence, the methods or the control system become very complicated, and it is practically impossible to carry out an assay making use of a magnetic material based on a very specific reaction or treatment process. As a result, the facility or the operating cost becomes very high.

10 In addition, in the method of gathering magnetic material based on the aforementioned conventional technology, it is difficult to position the magnet as described above in such a container as, for instance, a microplate, and even if possible, it is difficult to position a magnet on a side face of the container. It is also difficult to carry out the separation by attracting and gathering the magnetic material from a liquid, agitation and cleaning, and as a result it is extremely difficult to downsize the container by using a microplate, a fatal disadvantage.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for the control of the attraction and release of magnetic materials using a novel pipette. The most
20 remarkable feature of such method is that the capturing and gathering of the magnetic material diffused in a liquid from the liquid is not executed on the side of a container in which a specimen is accommodated but by a pipette which can take in and discharge the liquid containing the magnetic material. An assay which uses a magnet provided on the absorption/discharge side of a pipette tip or the like in this pipette device for the attraction and complete gathering of magnetic material in a short period of time can

result in the realization of a substantial improvement in measurement precision. A cross-contamination is prevented if a disposable pipette tip is used, and the method can easily respond to various types of assays based on a specific reaction or treatment process. An assay device using a magnetic material can be produced according to the invention, which has a simple construction and is easily operated, and also more versatile and low in cost.

To achieve the objects as described above, a magnet is provided in a liquid suction line in a pipette for sucking and discharging a liquid from inside a container. Any magnetic material in a liquid within the liquid suction line is bound and maintained on the internal surface of the liquid suction line due to magnetism of the magnet, and then the magnetic material is separated from the liquid suction line and discharged together with the liquid from the liquid suction line.

In the present invention, to enhance processing capability, a plurality of liquid suction lines may be provided in parallel to each other. Sucking or discharging a liquid in each liquid suction line is driven and controlled so that attraction of the magnetic material and the separation of the liquid from the magnetic material will be executed concurrently. This enables realization of a multi-channel system allowing concurrent processing of a plurality of specimens.

Furthermore, in the present invention, to enhance the processing capability and respond to any liquid requiring a specific treatment, it is possible to provide a plurality of liquid suction lines described above. Each liquid suction line may be controlled independently at a different timing so that suction and discharge of liquid are controlled to attract or separate the magnetic material mixed and diffused therein through a specific treatment.

In the present invention, at least one liquid suction line as described above is required. Improvement in processing capability can be achieved only by integrating a liquid suction line and a magnet into a unit and providing a plurality of units as described above along a container transfer line.

Also, in the present invention, the magnet described above includes any type of permanent magnet or electric magnet as far as anything that can generate magnetism for attracting a magnetic material, and one or more pieces of magnet can be provided in each liquid suction line in correspondence to the diameter of the liquid suction line, the quantity of the magnetic material to be attracted, and the size thereof.

- 10 Various modes for placing the magnets can be considered; for instance, magnets may be located in a direction in which a liquid flows in the liquid suction line or at opposite positions on both sides of the liquid suction line, or in the radial direction.

Furthermore, in the present invention, the above magnets can be located outside the liquid suction line, or directly on the liquid suction line.

- When locating magnets outside the liquid suction line as described above, a plurality of pieces of permanent magnet as the magnet bodies can be used and located on or near the liquid suction line. In this way, it is possible to bind and maintain the magnetic material contained in the liquid which is in the liquid suction line on the internal surface of the liquid suction line. It is further possible to discharge the
- 20 magnetic material together with the liquid from the liquid suction line by moving the magnet away from the liquid suction line to release the magnetic material from the line.

The magnets may be electromagnets on or near the liquid suction line which can bind and maintain magnetic material contained in liquid, sucked into the liquid suction line, on an internal surface of the liquid suction line. The electromagnets may be regulated by controls so as to reduce or eliminate their magnetism so as to

separate or release the magnetic material from the liquid suction line that the magnetism disappears or is reduced so as to discharge the magnetic material together with the liquid from the liquid suction line. To form such electromagnet, an exciting coil may be attached to the liquid suction line itself or the coil may be wound around the liquid suction line. A configuration may also be employed in which the electromagnet can be moved closer to or away from the liquid suction line.

In one aspect, the invention provides a liquid suction line formed by dismountably mounting a pipette tip onto an end section of the liquid sucking side thereof. The magnet body is arranged so as to enable magnetism to be generated
10 over magnetic material inside the pipette tip.

Thus when drawing in or discharging a liquid containing magnetic material with a pipette tip, the magnetic material can be captured as completely as possible onto the internal surface of the pipette tip. It is also possible to transfer a pipette tip with magnetic material deposited on an internal surface thereof, as is, to a further reaction or treatment step. This cannot be achieved without using the pipette device according to the present invention, and at least in that sense the present invention is novel.

The pipette tip described above is used repeatedly only for the same specimen only if specified or required for a particular assay to prevent cross-
20 contamination. Any number of pipette tips may be used for the same specimen according to the requirement for a reaction or a treatment process in various types of assays.

Also, in the present invention, if the liquid suction line is formed with a nozzle system in which a pipette tip cannot be loaded or unloaded, it is possible to separate the magnetic material from the liquid, agitate and clean the internal as well as

external surface of the liquid-contacting section in the liquid suction line by means of sucking or discharging the liquid to a degree where cross-contamination will not occur.

In the present invention, separation of magnetic material from a liquid is executed by discharging only the liquid from a liquid suction line in which the magnetic material is bound to the internal surface. This may be repeated by drawing up liquid into or discharging a liquid from the liquid suction line more than once. This is alternatively accomplished by inserting a pipette tip, with magnetic material attracted by a magnet body and bound onto an internal surface thereof, into liquid stored in another container and repetitiously drawing up and discharging the liquid to a state
10 where the magnetic material is not affected by the magnet described above.

Thus, it is possible to almost completely capture the magnetic material. The almost complete separation of magnetic material from a liquid containing the magnetic material can be realized in all processes requiring separation of magnetic material from a liquid containing it.

Also, in the present invention, when a pipette tip is mounted on a liquid suction line, the agitation and cleaning steps described above may be effected by transferring the pipette tip with bound magnetic material as is to the position for agitation and cleaning and then repeating the operations for drawing up and discharging the liquid. In this case, agitation and cleaning can be executed with the
20 magnetic material deposited on an internal surface of a pipette tip or drawing up and discharging the liquid one or more times to the point where the magnetic material is no longer affected by the magnet.

As described above, with the present invention, it is possible to homogeneously disperse the magnetic material in a liquid by sucking and discharging the liquid in a liquid suction line in a pipette device. It is also possible to improve the

cleaning efficiency; furthermore, the liquid containing the magnetic material does not splash out from the container containing the liquid. Hence, the agitation and cleaning processes can be executed under stable conditions without lowering the precision of measurement.

It should be noted that, according to the present invention, the separation of the magnetic material from the liquid and the above-mentioned agitation and cleaning of the magnetic material can be carried out by moving the magnet toward the liquid containing the magnetic material previously stored in a liquid storage section in a cartridge having a plurality of liquid storage sections and then sucking and discharging
10 the liquid according to need. Alternatively, while the magnetic material is deposited on an internal surface of a pipette tip, the residual liquid may be discharged out of the container, then, a liquid required for a next process may be poured into the same container and the liquid poured anew may be sucked up and then discharged with the pipette tip. In brief, according to the present invention, no specific form of a container is required for sucking and discharging a liquid in a liquid suction line to separate the magnetic material from the liquid, and to agitate and clean the magnetic material.

Another significant feature of the present invention is that it is possible to carry out both qualitative and quantitative measurements of a target material contained in a liquid by accurately controlling the quantity of the liquid drawn into a liquid suction
20 line.

The method according to the present invention is applicable to and effective in a reaction of a magnetic material and a liquid not containing any magnetic material and a physical or chemical deposit of a material present in a liquid onto a magnetic material. Such materials include immunological materials, biological materials, and molecular-biological materials such as antigens, antibodies, proteins,

enzymes, DNAs, vector DNAs, RNAs and plasmid. The method can be applied to assays and measuring instruments that employ labeling materials required for qualitative or quantitative analysis, e.g., isotopes, enzymes, chemiluminescent materials, fluorescent materials and electro-chemiluminescent materials or the like. The method according to the present invention can also be applied to apparatus for immunological assays, chemical assays, and extraction, recovery and separation of DNAs.

When the method according to the present invention is applied to an immunochemical measurement apparatus, the container may be formed by a cassette
10 having a plurality of liquid storage sections. A specimen or reagent required for reaction or processing may be poured into each liquid storage section in advance, and the container may be moved with a magnetic material attracted by the magnet to and deposited on an internal surface of a liquid suction line. In this case, the liquid is previously poured into each liquid storage section as described above, and only a portion thereof may be processed.

Furthermore, a specimen can directly be measured quantitatively, for instance, from a parent specimen container and then poured into the liquid storage section. It should be noted that the liquid storage sections in the cassette may be arranged either in a single array or in a plurality of arrays like a microplate. If the
20 cassette is formed like a microplate, a multi-channel system can be achieved by locating a plurality of liquid suction lines in correspondence to the liquid storage section arrays, and thus the processability can be substantially improved.

Other objects and features of this invention will become apparent from the following description with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow chart showing processes where the present invention is applied to an immunochemical assay involving a chemiluminescence method;

Figure 2 is a cross-sectional view showing an example of a pipette tip used in the present invention;

Figure 3 is an explanatory view showing an example of the general configuration that can be used for quantification in CLEIA;

Figure 4 is an explanatory view showing an example of the general configuration that can be used for quantification in CLIA;

10 Figure 5 is an explanatory view showing an example of the general configuration that can be used for quantification in EIA;

Figure 6 is an explanatory view showing an example of the arrangement of a magnet when the liquid suction line is a nozzle system;

Figure 7 is an explanatory view showing another example of an arrangement of a magnet in the present invention;

Figure 8 is an explanatory view showing still another example of an arrangement of a magnet in the present invention; and

Figure 9 is a flow chart showing processes in an immunochemical assay method based on the conventional type of chemiluminescence method.

20 DESCRIPTION OF THE PREFERRED EMBODIMENTS

Detailed description is made of the subject invention as applied to an immunochemical assay method based on chemiluminescence with reference to the attached drawings. However, the field of application of the present invention is not limited to this embodiment. The present invention can be applied to any situation

which uses a pipette device to attract/bind a magnetic material and release such material using a magnet.

A flow of an immunochemical assay according to the present invention as compared to a flow of the conventional type of immunochemical assay is described below with reference to Figure 1.

It should be noted that, in this embodiment, the magnetic material is such a material that can adhere to its surface an antigen or an antibody and be attracted by a magnet for B/F separation (separation of antigen/antibody complexes from other materials not bound to them).

10 In this figure, P indicates a pipette tip for pouring a specified quantity of a specimen from a parent vessel, such as a blood tube (not shown), into a specimen reaction container 1 and also for discharging into or sucking out of the specimen reaction container 1, a liquid containing a liquid-insoluble reactive magnetic material 3, a cleaning liquid 5, an enzyme-labeling liquid 6, a substrate liquid 7, a reaction termination liquid or the like.

As shown in Figure 2, the pipette tip P has three sections including a distal thinnest section 10 to be inserted into the specimen reaction container 1, a medium diameter section 11 having a larger diameter than the thinnest section 10, and a proximal large diameter section 12 having a larger diameter than the medium
20 diameter section 11. A magnet M for attracting the reactive liquid insoluble magnetic material 3 is detachably fitted to an external peripheral surface of the medium diameter section 11 with a mechanism for sucking or discharging a liquid into a cylinder or the like, the mechanism being detachably connected with and communicating with the top edge section of this pipette tip P. The form of this pipette tip P is not limited to that shown in this figure; any form is allowable on condition that, when a liquid is drawn into

the pipette tip P, any magnetic material contained in the liquid is captured by the magnet M without fail. To completely capture the magnetic material with the magnet, however, it is desirable that the section contacted by the magnet have a small diameter. This is also preferable for the efficient control of flow rate while drawing up or discharging a liquid.

It should be noted that, when extracting, recovering, or separating DNAs, a molded pipette tip having a large diameter is desired to prevent the DNAs from being broken or damaged due to movement of the magnetic material when the liquid is drawn up or discharged.

10 In the specimen reaction container 1 shown in Figure 1, a plurality of liquid storage sections 1A through 1H are provided in a straight array, in a loop, or in a zig-zag form with a roughly specified quantity of a specimen having been poured in the liquid storage section 1A, a specified quantity of a reactive liquid-insoluble magnetic material liquid 3 in the liquid storage section 1B, a specified quantity of a cleaning liquid 5 in the liquid storage sections 1C and 1D, a specified quantity of a labeling liquid in the liquid storage section 1E, a specified quantity of a cleaning liquid 5 in the liquid storage sections 1F and 1G, each filled with the liquid before the start of the assay, and a substrate liquid in the liquid storage section 1H for measurement of the luminescence.

20 In the case of the CLIA or CLEIA assay, the specimen reaction container 1 is made of an opaque material to prevent any effect by luminescence, and in the case of the EIA assay, at least the bottom section is made of a transparent material.

When carrying out immunochemical assays according to the present invention using the specimen reaction container 1 constructed as described above a

specified quantity of the specimen in the liquid storage section 1A is drawn up with the pipette tip P for quantitative analysis.

Then, the pipette tip P containing the specimen is moved relative to the container and all of the specimen in the pipette tip P is discharged into the liquid containing a reactive liquid-insoluble magnetic material 3 in the liquid storage section 1B. To create a homogeneous mixture of the insoluble magnetic material in the specimen, the mixture of the specimen and the reactive liquid-insoluble magnetic material liquid 3 is repeatedly drawn up and discharged with the pipette tip P (this operation is called liquid drawing up/discharge hereinafter). After several hours of incubation, all or a specified part of the incubated mixed liquid is drawn up with the pipette tip P.

The magnetic material 2 floating in the mixed liquid sucked by the pipette tip P is captured onto the internal wall surface of the medium diameter section 11 due to magnetism of the magnet M provided outside the pipette tip P, as shown in Figure 2, when the mixed liquid passes through the medium diameter section 11. The mixed liquid is drawn into the pipette tip P to the height shown in Figure 2, so that, when all the mixed liquid is sucked into the pipette tip, the bottom face x comes near a lower edge of the magnet M or to a level higher than that and the magnetic material 2 is completely captured.

After all the magnetic material 2 has been captured, the remaining liquid is discharged into the liquid storage section 1B, and only the magnetic material 2 remains in the pipette tip P. As the magnetic material 2 is wet then, the magnetic material 2 is kept deposited on the internal surface of the medium diameter section 11 of the pipette tip P; so that, even if the pipette tip is moved, the magnetic material rarely drops off from the internal surface. Then the pipette tip P is then moved to the

next liquid storage section 1C with the magnetic material 2 captured therein, and the cleaning liquid 5 is drawn into the liquid storage section 1C. Then the magnet M is moved away from the pipette tip P such that the magnetic material 2 is released into the cleaning liquid. By drawing up and discharging the cleaning liquid 5, all the magnetic material 2 can efficiently be cleaned. The drawing up and discharging of the cleaning liquid may be repeated as often as is necessary.

Finally, all the cleaning liquid 5 from the liquid storage section 1C is slowly drawn into the pipette tip P (over a period of 5 to 10 seconds). Then the magnet M is again moved toward the pipette tip P to capture all the magnetic material 2 floating in the drawn up cleaning liquid 5. The cleaning liquid 5 is then discharged into the liquid storage section 1C, so that only the magnetic material 2 remains in the pipette tip P.

Then the cleaning liquid 5 in liquid storage section 1D is drawn up into the pipette tip P. The operations for cleaning and capturing the magnetic material 2 are conducted according to the same sequence as described above for liquid storage section 1C.

Then the labeling liquid 6 in the liquid storage section 1E is drawn up into the pipette tip P. Then the magnet M is moved away from the pipette tip P to release the magnetic material 2, into the labeling liquid. By drawing up and discharging the labeling liquid 6, all the magnetic material 2 can be homogeneously reacted with the labeling liquid 6.

Incubation is carried out for a specified period of time, and then all the labeling liquid 6 in the liquid storage section 1E is slowly drawn into the pipette tip P (for instance, over a period of 5 to 10 seconds). Then the magnet M is once again positioned near the pipette tip P so that all the magnetic material 2 floating in the

drawn up labeling liquid 6 is captured. The labeling liquid 6 is then discharged into the liquid storage section 1E, and only the magnetic material 2 remains in the pipette tip P.

Then the cleaning liquid 5 in the liquid storage section 1F is drawn up into the pipette tip P. The operations for cleaning and capturing the magnetic material 2 are executed according to the same sequence as described above for liquid storage sections 1C and 1D. Then the cleaning liquid 5 in the liquid storage section 1G is drawn up into the pipette tip P. Then the operations for cleaning and capturing the magnetic material 2 are performed in the same sequence as described above with respect to the cleaning liquid in the liquid storage section 1F.

10 Then the pipette tip P is transferred to the liquid storage section 1H. For instance, if a measurement is required in which a certain period of time is required until the rate of light emission is stabilized after mixture with a substrate liquid such as the CLEIA assay, the substrate liquid 7 previously stored in the liquid storage section 1H is drawn up by the pipette tip P. Then the magnet M is moved away from the pipette tip P and the magnetic material 2 is released, so that it is possible to homogenize the reaction between the magnetic material 2 and the substrate liquid 7 by drawing up and discharging the substrate liquid 7.

20 When the operations for drawing up and discharging the liquid have been completed and the liquid has been incubated for a certain period of time, a quantity of emitted light is measured by the optical measurement instrument 9 such as a PMT as shown in Figure 3.

In the case of an assay method in which luminescence continues only for a very short period of time, such as the CLIA assay, the liquid storage section 1H is provided as shown in Figure 4. A filter 16 and a water-absorbing pad 20 are provided in the liquid storage section 1H, and the magnetic material 2 is discharged together

with the cleaning, liquid 5 previously drawn into the pipette tip P, into the liquid storage section 1H such that the magnetic material 2 is captured by the filter 16. Then a liquid which triggers light-emission, such as hydrogen peroxide liquid (H_2O_2), is supplied from a nozzle 17 so that the magnetic material emits light. The quantity of light emitted when the substrate liquid is poured may be measured with an optical measurement instrument 9 such as a PMT.

In the case of EIA assays, after the substrate liquid 7 is poured, a reaction stop liquid is supplied and as shown in Figure 5 the resulting mixture is irradiated with light of a specified wavelength from a bottom section of the liquid storage section 1H, and the absorbance is measured by a light-receiving element and a detector at a specific wavelength.

Thus, with the specimen reaction container 1 according to the present embodiment, it is possible to accommodate a number of types of immunochemical assays by changing only the configuration of the liquid storage section 1H to correspond to the requirements of an individual assay method. Thus, versatility can substantially be improved. Also, a multi-channel system of this type can be achieved by providing liquid storage sections arranged in arrays in the specimen reaction container 1 such that the form resembles a microplate.

The pipette tip P and the specimen reaction container 1 may be disposed after use.

It should be noted that, although in the description of the embodiment described above the specimen reaction container 1 is cleaned twice after the reaction insoluble magnetic material liquid 3 is discharged and furthermore 2 times after the labeling liquid 6 is discharged, the present invention is not limited to the configuration

described above: the specimen reaction container 1 may be cleaned any number of times according to need.

Also the above description describes a configuration in which the pipette tip P is transferred to each liquid storage section in the specimen reaction container 1, but a configuration is allowable in which the pipette tip P is moved only in the vertical direction and the specimen reaction container 1 is intermittently transferred for executing each of the operations described above.

Furthermore, the description of the above embodiment describes a case where the pipette tip P and the specimen reaction container 1 are disposable, although
 10 a configuration is allowable where the pipette tip P and the specimen reaction container 1 can be cleaned and used repeatedly. Also, the description of the above embodiment describes a case in which the waste liquid, after being drawn up by the pipette tip P, is recycled to the original liquid storage section from which the liquid was drawn. A configuration is also allowable, however, where the waste liquid is returned to a waste liquid section provided outside the specimen reaction container 1.

The present invention is applicable to cases where the pipette tip P is not used and a liquid suction line is formed as a nozzle system. In this case, the configuration as shown in Figure 6 is allowable where a lower section P_A of the liquid suction line P_1 forms a thin diameter section, and the magnet M or an electromagnet is
 20 moved to or away from the lower section P_A of the liquid suction line P_1 . When using the electromagnet, a configuration is allowable where the electromagnet is fitted to the thin diameter section of a liquid suction line or the electromagnet is directly wound around the thin diameter section of the liquid suction line and operations for separating the magnetic material from the liquid, agitation, and cleaning are executed by turning ON or OFF a current.

Also, the description of the embodiment above assumes a case where the magnet M is detachably fitted to one side of the medium diameter section 11 of the pipette tip P, the magnets M may be provided on both sides of the medium diameter section 11 as shown in Figure 7. Also, a plurality of magnets M may be provided in a radial form around the medium diameter section 11 shown in Figure 8, and also a plurality of magnets may be provided along the longitudinal direction of the medium diameter section 11, although that case is not shown herein.

As described above, in the present invention, magnetic material is loaded or unloaded by making use of a pipette device, and the magnetic material is collected
10 not on the side of a container in which a liquid is stored, but on the side of a liquid suction line for sucking and discharging a liquid containing magnetic material by making use of a magnet provided therein, so that the magnetic material can be almost completely captured within a short period of time.

Also, in the present invention, a multi-channel system in which a plurality of specimens can be processed concurrently by providing a plurality of the liquid suction lines described above and controlling the operations for drawing up and discharging a liquid so that each liquid suction line absorbs or releases magnetic material at the same timing respectively is contemplated. In this way, the processing capability can be enhanced.

20 Furthermore, in the present invention, various types of liquid each requiring distinct processing can be accommodated by providing a plurality of liquid suction lines described above and controlling each of the liquid suction lines so that magnetic material is absorbed or released by drawing up or discharging each liquid containing the magnetic material independently. Timing can be adjusted

independently for each liquid according to the specific process required for each liquid. In this way, the processing capability can be enhanced.

The processing capability can be further enhanced by integrating a liquid suction line and a magnetic body into a unit and providing a plurality of units along the container transfer line.

In the present invention, when a liquid containing magnetic material is drawn up or discharged, the magnetic material is attracted to an internal surface of the pipette tip, so that the magnetic material can be almost completely collected, and the pipette tip can be transferred to the next reaction process or processing step with the
10 magnetic material deposited on the internal surface thereof.

The pipette tip is repeatedly used only for the same specimen in a process in which a specimen is processed according to a specified assay method, so that cross-contamination can be prevented. If the liquid suction line is based on a nozzle system in which a pipette tip is not loaded or unloaded, it is possible to prevent cross-contamination by cleaning an internal surface of the liquid suction line by drawing up and discharging a liquid.

Furthermore, in the present invention, operations for separating magnetic material from a liquid, agitation, and cleaning are executed by drawing up and discharging the liquid with the cleaned liquid suction line described above once or
20 more, so that the magnetic material can be almost completely collected. In addition, in the present invention, the operations of agitating and cleaning the magnetic material are executed, as described above, on the side of a liquid suction line of a pipette device by drawing up and discharging a liquid, so that the magnetic material can be homogeneously diffused in the liquid, and also to improve the cleaning efficiency. In addition, although drawing up and discharge of the liquid is executed between the

liquid suction line and a container, the liquid containing the magnetic material never splashes out. As a result, the operations of agitation and cleaning can be stabilized and precision in measurement does not become low due to contamination by the splashing out of the liquid containing the magnetic material.

In the present invention, the quantity of liquid to be drawn up can be controlled by the liquid suction line accurately, so that both qualitative and quantitative analysis of a target material contained in a liquid can be carried out with high precision.

Furthermore, the method according to the present invention can be applied to various types of apparatus, and in this case the mechanism required for
10 controlling the magnetic material can be substantially simplified. As well, the precision in measurement can be substantially improved and stabilized.

Although the invention has been described with respect to a specific embodiment for a complete and clear disclosure, the appended claims are not to be thus limited but are to be construed as embodying all modifications and alternative constructions that may occur to one skilled in the art which fairly fall within the basic teaching herein set forth.

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CLAIMS:

1. A method for controlling attraction and release of a magnetic material, which comprises:

(A) providing (i) a liquid suction line having a liquid inlet end and (ii) at least one magnet fitted to an external peripheral surface of the liquid suction line;

(B) sucking, from a container through the liquid inlet end into the liquid suction line, a first liquid containing the magnetic material which is insoluble in the liquid, thereby attracting the magnetic material on an internal surface of the liquid suction line due to magnetism of the magnet;

(C) discharging the sucked liquid alone through the liquid inlet end out of the liquid suction line, while maintaining the magnetic material attracted to the internal surface of the liquid suction line due to the magnetism of the magnet;

(D) sucking through the liquid inlet end into the liquid suction line, a second liquid that is the same or different from the first liquid; and

(E) discharging the second liquid through the inlet end out of the liquid suction line alone or together with the magnetic material, wherein when only the second liquid is

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discharged, the magnetic material is maintained attracted to the internal surface of the liquid suction line and when the second liquid is discharged together with the magnetic material, the magnetic material is released from the internal
5 surface of the liquid suction line by interrupting the magnetism.

2. The method according to claim 1, wherein a plurality of the liquid suction lines are provided in parallel to each other and the steps (B) through (E) are
10 driven and controlled so that the magnetic material is concurrently sucked and discharged at the same time.

3. The method according to claim 1, wherein a plurality of the liquid suction lines are provided in parallel to each other, and each of the liquid suction lines
15 is driven and controlled so that the liquid in each liquid suction line is sucked and discharged independently at a different time and through a specific process to each liquid suction line to attract or release magnetic material.

4. The method according to claim 1, wherein the liquid
20 suction line and the magnet are integrated into a unit and a plurality of the units are provided along a container transfer line.

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5. The method according to claim 1, wherein one or a plurality of the magnets are provided on the liquid suction line.
6. The method according to claim 1, wherein the magnet
5 is provided outside the liquid suction line.
7. The method according to claim 1, wherein the magnet is mounted on the liquid suction line.
8. The method according to any one of claims 1 to 7, wherein the magnet is a permanent magnet and the magnetic
10 material contained in the liquid sucked into the liquid suction line is absorbed and deposited on the internal surface of the liquid suction line by moving the magnet closer to the liquid suction line; and the magnetic material is discharged together with the second liquid out of the
15 liquid suction line by moving the magnet away from the liquid suction line.
9. The method according to any one of claims 1 to 7, wherein the magnet is an electro-magnet and the magnetic material contained in the liquid sucked into the liquid
20 suction line is absorbed and maintained on the internal surface of the liquid suction line by generating magnetism

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with the electro-magnet; and the magnetic material is discharged together with the second liquid from out of the liquid suction line by eliminating or reducing the magnetism generated by the electro-magnet.

5 10. The method according to any one of claims 1 to 9, wherein the liquid suction line is a part of a pipette device having a pipette tip which is dismountably mounted onto a tip section of the liquid suction line.

11. The method according to claim 10, wherein the
10 pipette tip is transferred to a specific processing position according to each inspection method with the magnetic material absorbed and maintained onto the internal surface thereof.

12. The method according to claim 10, wherein the
15 pipette tip is repeatedly used only with respect to the same specimen.

13. The method according to claim 10, wherein the second liquid employed in step (D) is a cleaning liquid; and in step (E), the second liquid containing therein the
20 magnetic material is sucked in and discharged out of the liquid suction line repeatedly without magnetism to agitate

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and clean the magnetic material to a degree at which cross contamination does not occur.

14. The method according to claim 1, wherein the second liquid employed in step (D) is a cleaning liquid; and the sucking step (D) and the discharging step (E) are conducted one or more for agitation and cleaning of the magnetic material.

15. The method according to claim 14, wherein only the cleaning liquid is discharged in step (E) with the magnetic material kept attracted by the magnet.

16. The method according to claim 14, wherein the sucking and discharging steps (D) and (E) are repeated while these operations are not affected by the magnetism.

17. The method according to claim 14, wherein the liquid suction line is a part of a pipette device having a pipette tip; and after the pipette tip is transferred to a cleaning position with the magnetic material attracted onto the internal surface of the pipette tip by the magnet, the sucking and discharging steps (D) and (E) of the cleaning liquid are repeated.

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18. The method according to claim 14, wherein the sucking and discharging steps (D) and (E) are conducted while the magnetic material is attracted onto the internal surface of the liquid suction line.

5 19. The method according to claim 18, wherein the magnetic material has a surface coated with an antigen or antibody.

20. The method according to claim 14, wherein the cleaning liquid is previously stored in a liquid storage
10 section of a cartridge.

21. The method according to claim 14, wherein the liquid suction line is a part of a pipette device having a pipette tip; and the cleaning liquid is discharged in step (E) outside of a container while the magnetic material
15 deposited on the internal surface of the pipette tip, then a liquid required for a next processing is poured into the same container, and the poured liquid is sucked and discharged with the pipette tip.

22. A precise method for qualitative or quantitative
20 analysis of a target object comprising the step of:
providing a pipette device having a liquid suction

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line, and one or more magnet bodies fitted to an external peripheral surface of the liquid suction line of the pipette device;

completing a plurality of sucking and discharging
5 steps of a liquid containing the target object, wherein the magnet bodies attract or release a magnetic material; and
performing a quantitative or qualitative analysis
of the target object.

23. An analyzer using a magnetic substance
10 attracting/releasing control method making use of a pipette device, wherein the pipette device comprises a liquid suction line including a liquid inlet end for sucking a liquid containing the magnetic substance from a container and discharging the liquid through the liquid inlet end, a magnet
15 body or magnet bodies being fitted to an external peripheral surface of the liquid suction line.

24. An analyzer according to claim 23, wherein the analyzer executes processing based on an immunochemical measurement method.

20 25. An analyzer according to claim 24, wherein a container is formed into a cassette-like having a plurality of liquid storage sections, liquid and specimens are

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previously poured into each of the liquid storage sections according to a necessity in reaction or processing, and the container is transferred with the magnetic material deposited on an internal surface of a liquid suction line by a magnetic
5 force generated by the magnet body.

26. An analyzer according to claim 24, wherein the container is formed into a form like a microplate having a plurality of liquid storage sections provided and arrayed therein.

10 27. A method of analyzing a target material contained in a liquid substance using a pipette device having a liquid suction line including a liquid inlet end for sucking a liquid containing a magnetic material from a container to a reservoir and discharging the liquid through the liquid inlet
15 end, a magnet body or magnet bodies fitted to an external peripheral surface of the liquid suction line thereof, comprising the steps of:

(a) mixing the liquid substance with the magnetic material in a container,

20 (b) transferring the mixture from the container to the reservoir of the pipette means,

(c) repeatedly applying a magnetic field to the reservoir and removing the magnetic field from the reservoir,

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(d) transferring the magnetic material from the reservoir to a container to produce a test mixture, and

(e) thereafter, testing the test mixture to analyze the target material extracted with the magnetic material.

28. The method of claim 27, wherein said step (a) comprises transferring a first predetermined amount of the liquid substance from a first vessel to the reservoir of the pipette means.

29. The method of claim 28, wherein said step (a) further comprises discharging a first predetermined amount of the liquid substance from the pipette means to a second vessel comprising a second predetermined amount of the magnetic material.

30. The method of claim 29, wherein the magnetic material comprises insoluble magnetic material suspended in the liquid.

31. The method of claim 27, wherein said step (c) further comprises repeatedly transferring the magnetic mixture from the pipette means to the container and from the container to the pipette means to agitate the magnetic mixture until the magnetic material has homogeneously mixed with the liquid substance.

32. The method of claim 31, wherein the magnetic mixture is transferred from the pipette means to the container and from the container to the pipette means while the magnetic

field is applied to the pipette means.

33. The method of claim 32, wherein a magnet is provided outside the pipette means to produce the magnetic field.

34. The method of claim 32, wherein the magnetic field is applied to accumulate the magnetic material on an inside wall of the reservoir.

35. The method of claim 32, wherein said step (c) further comprises discharging the liquid substance to the container when the magnetic material is accumulated on the inside wall of the reservoir.

36. The method of claim 35, wherein said step (c) further comprises transferring cleaning liquid from a third vessel to the reservoir after discharging the liquid substance.

37. The method of claim 36, wherein said step (c) further comprises removing the magnetic field after the cleaning liquid is transferred to the reservoir.

38. The method of claim 37, wherein said step (c) further comprises cleaning the magnetic material by transferring the cleaning liquid and the magnetic material from the reservoir to the third vessel and from the third vessel to the reservoir when the magnetic field is removed.

39. The method of claim 38, further comprising applying a magnetic field after the step of cleaning to accumulate the magnetic material on the inside wall of the reservoir and discharging the cleaning liquid.
40. The method of claim 39, wherein said step of cleaning is repeated more than once.
41. The method of claim 40, wherein said step (c) further comprises transferring labeling liquid from a fourth vessel to the reservoir after discharging the cleaning liquid.
42. The method of claim 41, wherein said step (c) further comprises labeling the magnetic material by transferring the labeling liquid and the magnetic material from the reservoir to the fourth vessel and from the fourth vessel to the reservoir when the magnetic field is removed.
43. The method of claim 42, wherein the magnetic field is applied after the step of labeling to accumulate the magnetic material on the inside wall of the reservoir and then discharging the labeling liquid.
44. The method of claim 43, wherein the step of cleaning is repeated after the step of labeling.
45. The method of claim 44, wherein said step (d) comprises transferring substrate liquid from a fifth vessel to

the reservoir when the magnetic field is applied.

46. The method of claim 45, wherein the step (d) further comprises discharging the substrate liquid and the magnetic material from the reservoir to the fifth vessel when the magnetic field is removed, to produce the test mixture.

47. The method of claim 27, wherein the step (e) comprises measuring light emitted by the test mixture.

48. The method of claim 47, wherein the liquid substance comprises a light-emitting trigger liquid.

49. The method of claim 47, wherein the liquid substance comprises hydrogen peroxide.

50. The method of claim 46, wherein the container comprises the first, second, third, fourth and fifth vessels.

51. Apparatus for performing chemiluminescence inspection comprising:

a container,

a pipette device for transferring a mixture of liquid to be measured and magnetic material from the container to a reservoir in the pipette device, and

a magnet device provided outside the pipette device for applying magnetic field to the reservoir, the magnet device periodically applying the magnetic field to accumulate the

magnetic material on an inside wall of the reservoir and removing the magnetic field to allow the magnetic material to be transferred to the container.

52. The apparatus of claim 51, wherein said reservoir comprises a first portion inserted into the container, a second portion having a larger diameter than the first portion, and a third portion having a larger diameter than the second portion.

53. The apparatus of claim 52, wherein said magnet device is provided adjacent to the second portion of the reservoir to accumulate the magnetic material on the inside wall of the second portion.

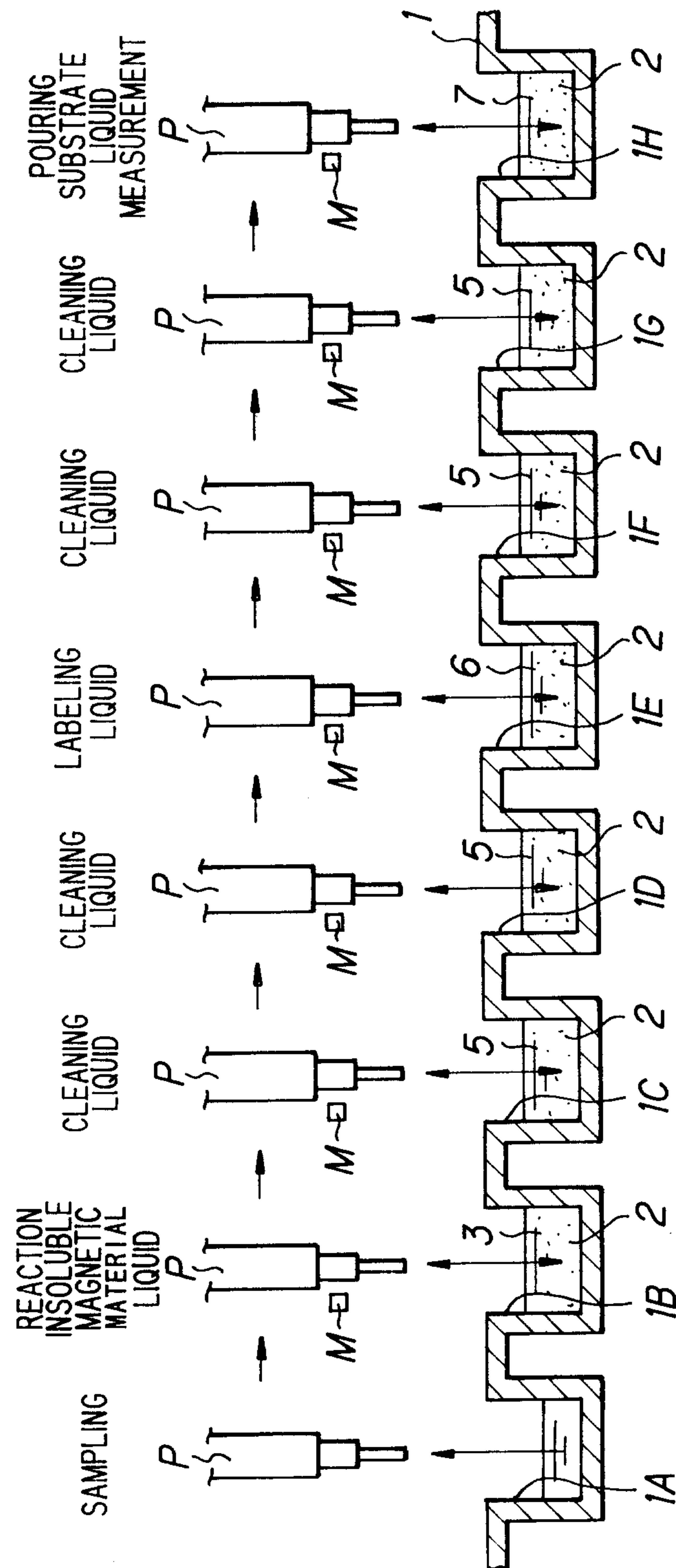
54. The apparatus of claim 53, wherein the pipette device further comprises a mechanism for transferring the liquid to and from the container.

55. The apparatus of claim 54, wherein said mechanism is attached to the third portion of the reservoir.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

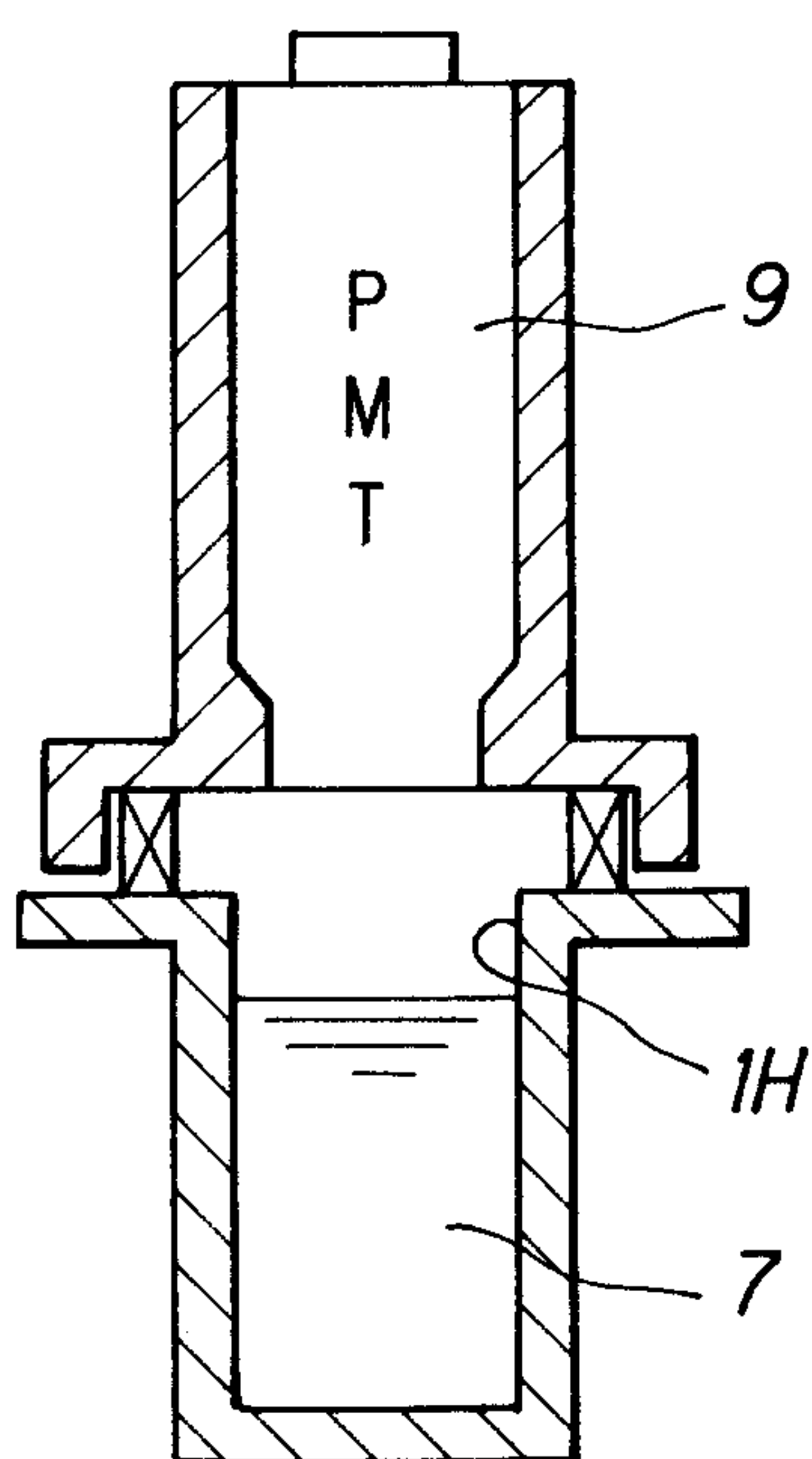
FIG. 1



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FIG. 3



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FIG. 4

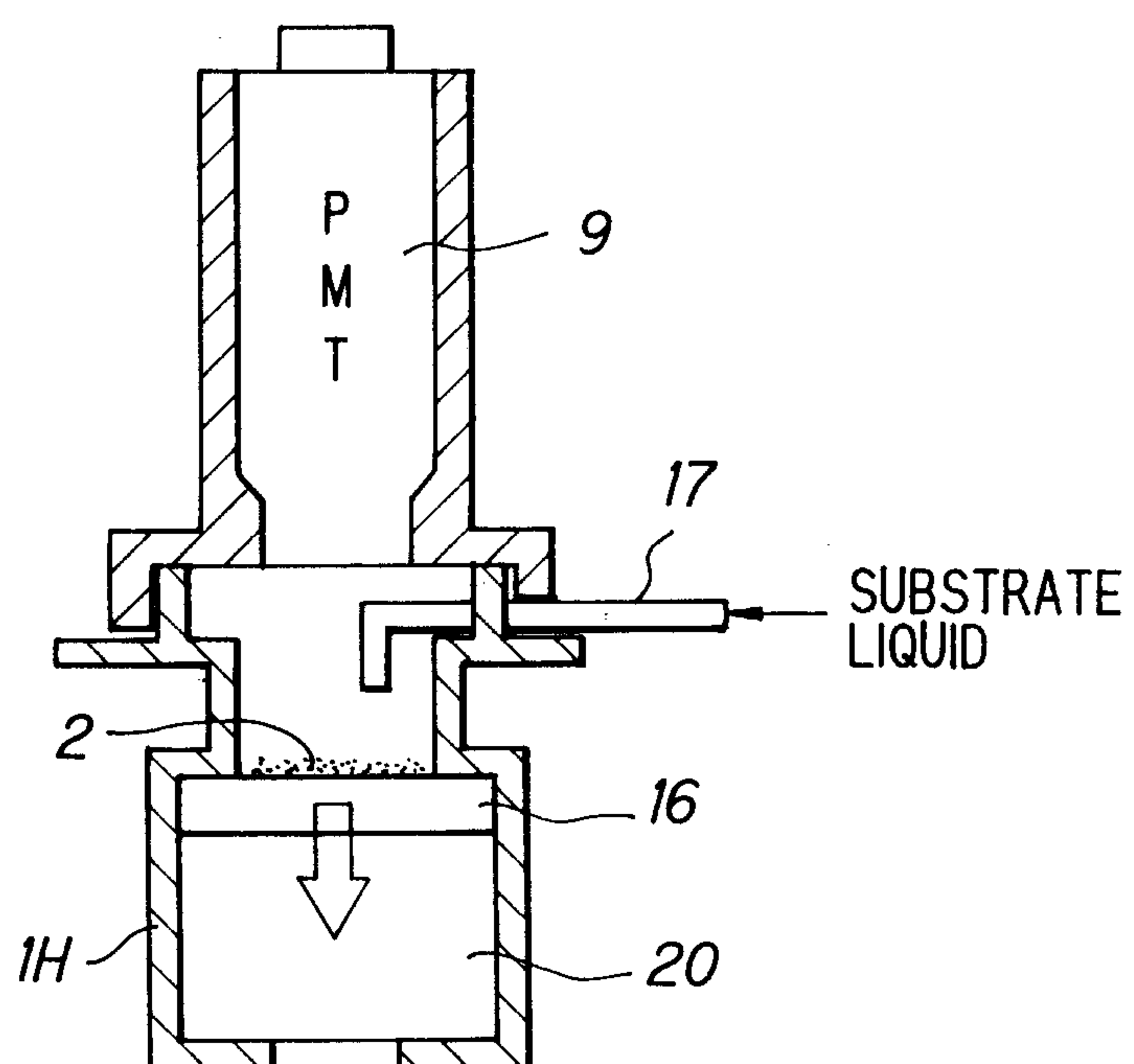


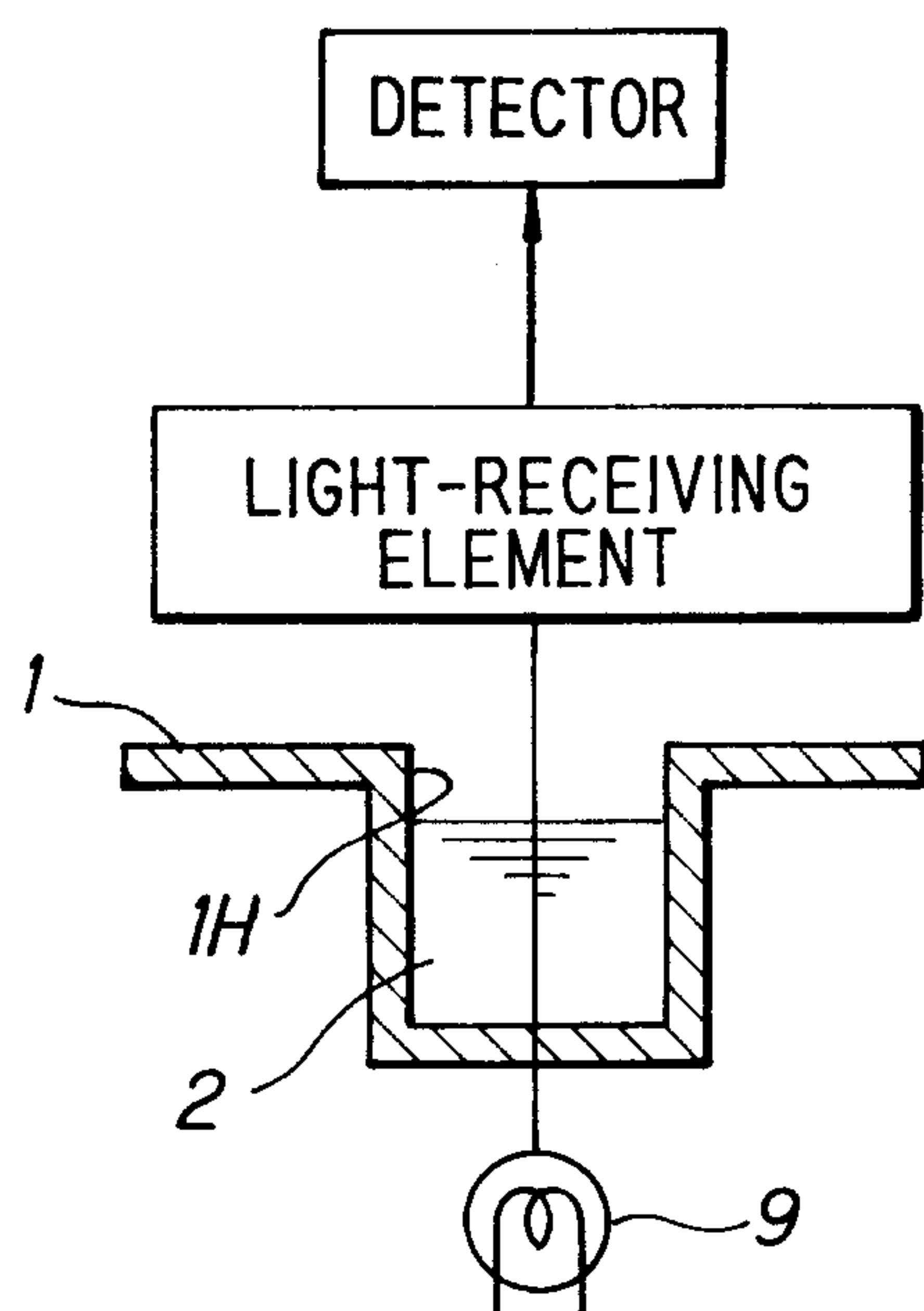
FIG. 5

FIG. 6

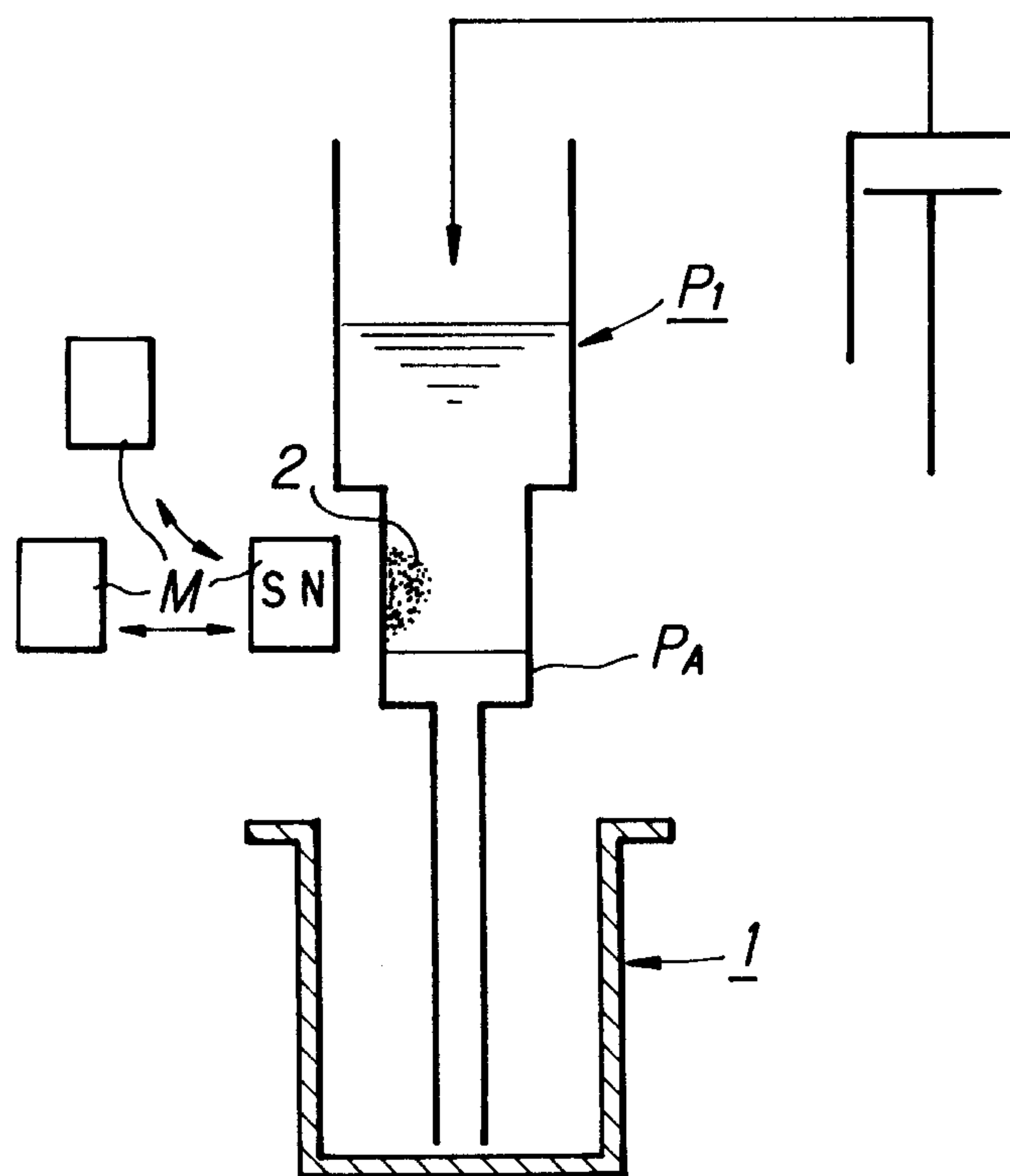


FIG. 7

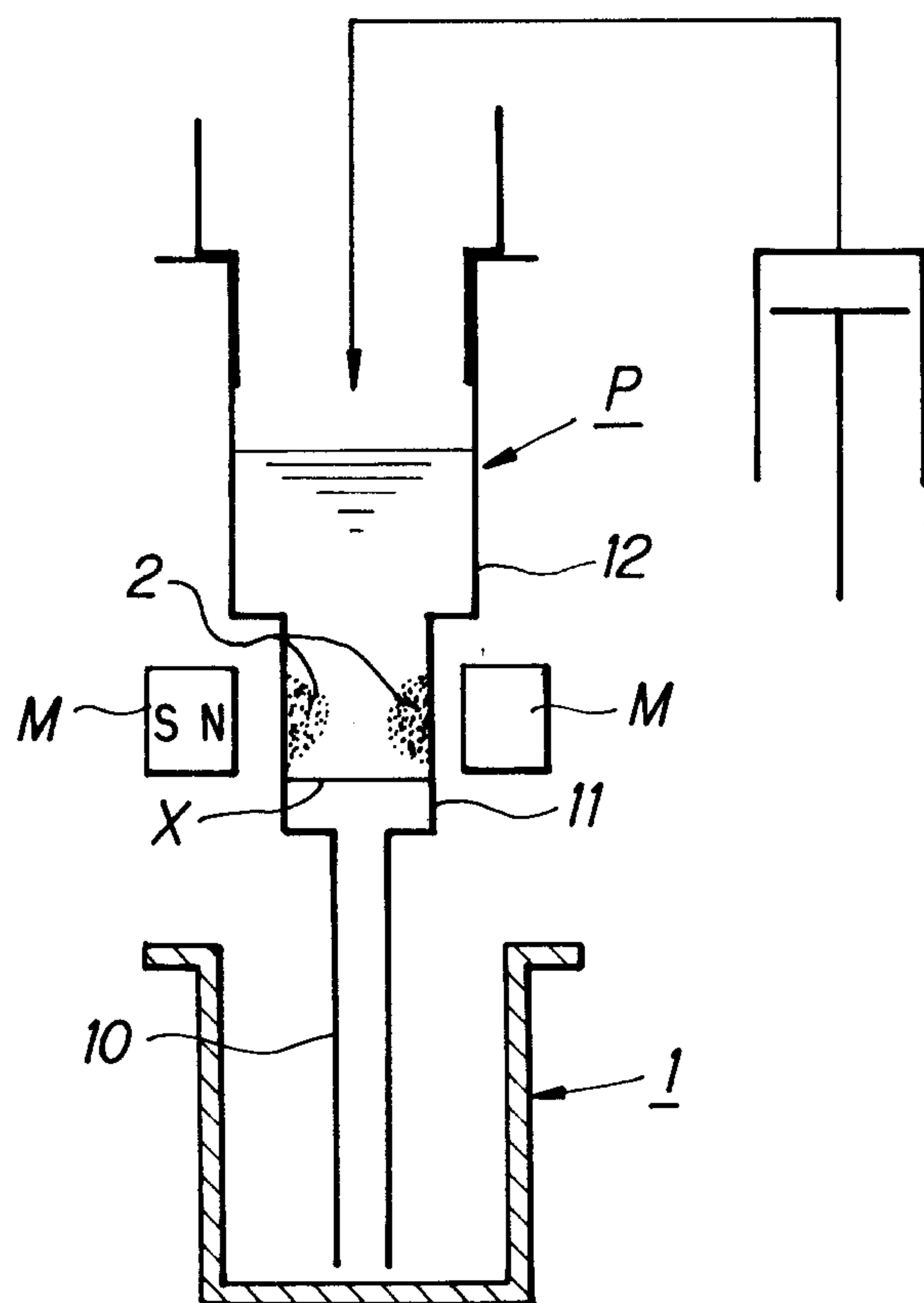
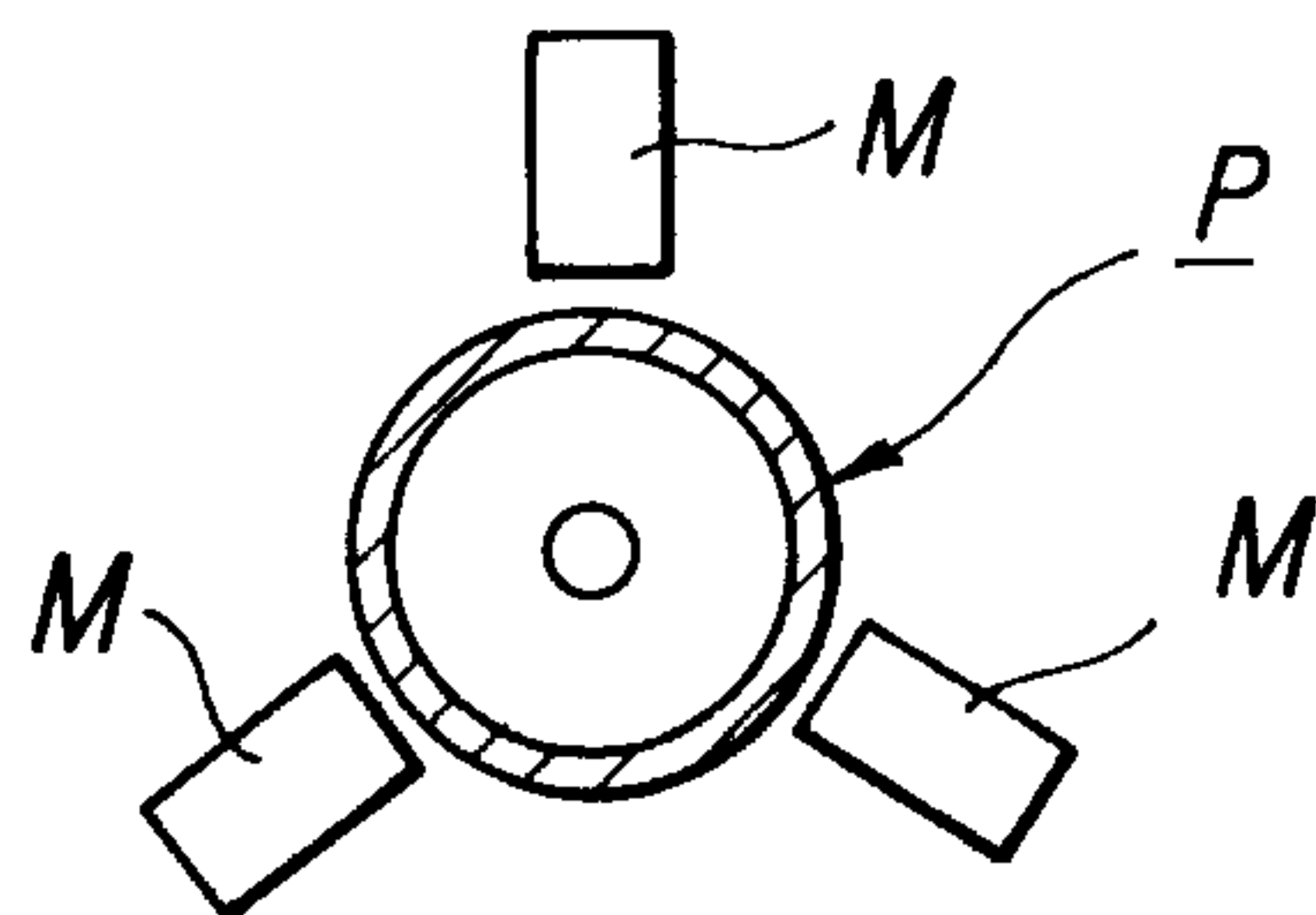


FIG. 8



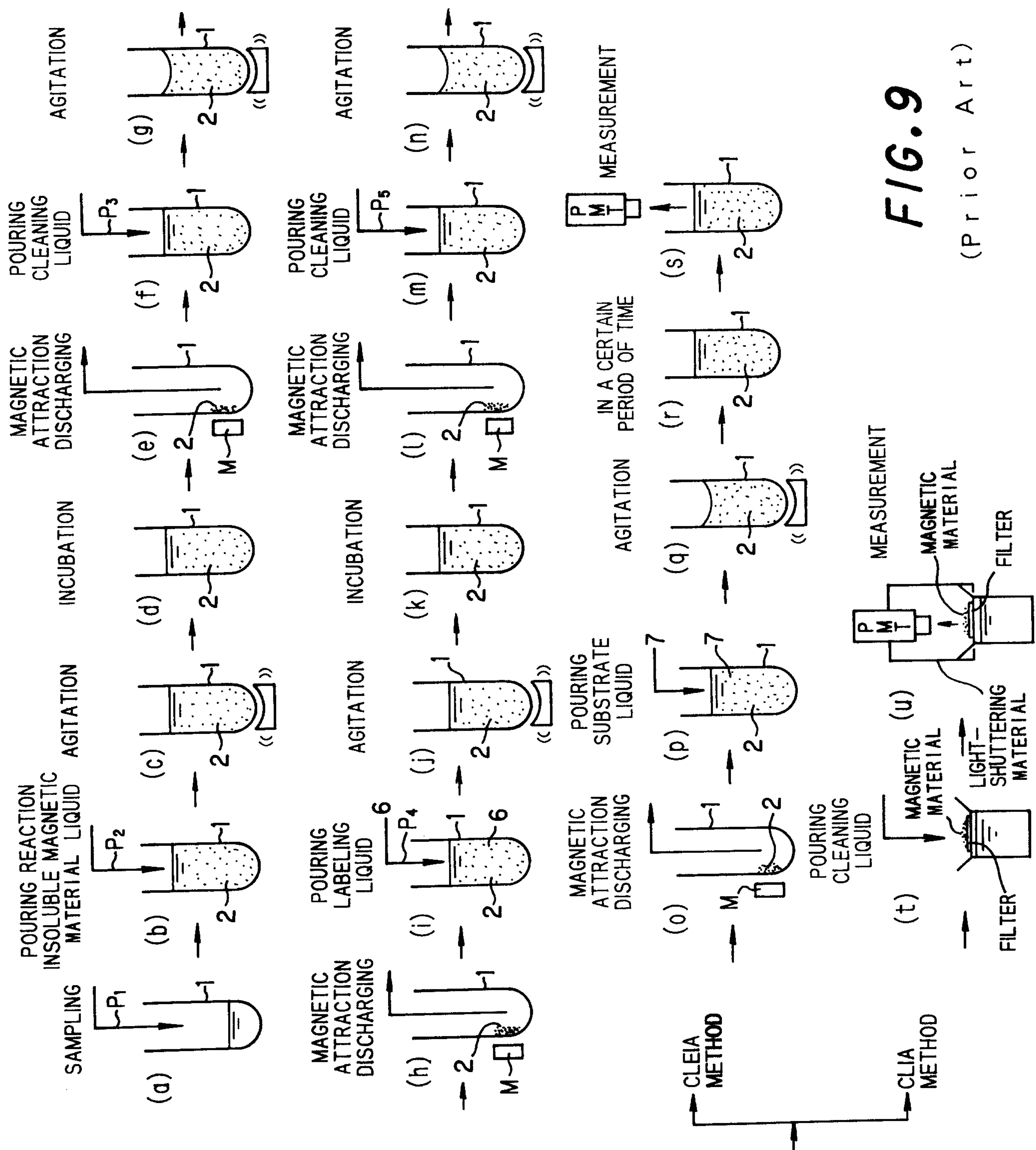


FIG. 9

(Prior Art)

