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**NL-2596 HG Den Haag(NL)**(54) **Thermostatic device for sample supports.**

(57) A device for thermostating a microtiter plate (25) in which the edge of the microtiter plate cooperates with the edge of a receptacle (8) to form a compartment between the receptacle and the microtiter plate, which compartment has a feed connection (14,10,11,12) with a thermostated reservoir (1) and drains (23,24) to said reservoir and a valve (13) to interrupt the connection, which valve preferably is linked to a fixing means (20,21,22) for the microtiter plate.

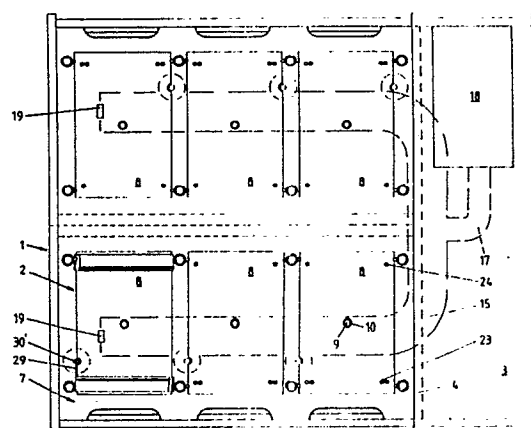


FIG. 1

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### Device for bringing and keeping a sample support at a predetermined temperature.

The invention relates to a device with one or more receptacles adapted to receive a sample support having a plate with a plurality of downwardly directed recesses, such as a so-called microtiter plate, which device is provided with means for maintaining a heat carrying liquid in a liquid store on a controlled temperature and duct means connected between the store and the receptacles.

Such a device is known from the Dutch patent specification NL-C-173 066.

With this known device a plate which cooperates with a sample support in the form of a microtiter plate is heated to a predetermined temperature. Herewith for heat transfer from the liquid onto the sample support a transfer is necessary from the plate heated by the liquid unto the sample support. In practice this leads to delays in heating the samples in the sample support. Also for this reason the moment at which the samples attain the desired temperature is determined in a less accurate way. In this connection it is important that in microbiology, enzymology and immunology with many applications, such as kinetic studies, phenomena are studied, which are dependent on time as well as on temperature.

The invention aims to provide a device with which the samples can be brought to temperature in a considerable faster way, so that also the moment at which the desired temperature is attained is determined more accurately.

The above aim is attained by the invention by providing that the receptacles and/or the sample support are provided with sealing means to form a sealed compartment between the receptacle and the plate of the sample support and that the duct means contain a connection from the liquid store to the said compartment and a drain from said compartment to the liquid store, at least one of the connections and the drain being provided with closable valve means.

In this connection it is pointed to it, that having a temperature controlled medium flowing around the samples is known per se from for instance the Dutch Patent Application NL-A-73 08785 or the European Patent Application EP-A-0 236 957. Here, however, the medium is air, by reason of which bringing to temperature occurs more slowly than with temperature control by means of a thermostated liquid, whereas moreover for the same temperature change considerably greater volumes have to be transported.

Further heating of an incubator by bringing a sample support in a closed space, which is heated and in which an air circulation is maintained, is known from the European Patent Application EP-A-

0 238 313.

US-A-3 505 023 shows a sample support having an upper surface with downwardly extending depressions for receiving samples, and a temperature conditioning fluid chamber below said surface, which chamber is provided with a fluid inlet and outlet. Connecting these in- and outlets to a hose or suchlike duct is rather cumbersome and leads to complicated connection structures in case of a considerable number of sample supports. Further bringing the samples into the depressions has to be done in situations, in which the inlet and the outlet impede somewhat the free access to the depressions, whereas emptying the chamber seems desirable in case quick heating to the desired temperature is necessary.

In Patent Abstracts of Japan, Vol. 7, no. 278(P-242)(1423) a thermostatic chamber of automatic biochemical analyser has been shown in which reaction cassettes from which sample containing tubes protrude downwardly are moved on side plates, a current of thermostated air flowing in the direction transverse to the movement of the cassettes. Apart from the relatively slow temperature changes to be realized by a gas stream this analyser has the disadvantages, that samples only can be added in agreement with the working speed, that all samples have to be subjected to the same duration of treatment and that the tubes have to be inserted individually into the cassettes.

Finally the use of microtiter plates in a device for heating samples for microbiological purposes is known from the European Patent Application EPA-A-0 063 744, in which the microtiter plate is placed on a plate which is cooled by means of a liquid and the heat given off by an electromotor is dissipated by means of a blower.

By application of the invention further a device is obtained which is easy to handle, if according to a further feature of the invention the receptacles have a surface with a border, which forms a seal with an edge of the sample support. A preferred embodiment hereof exists in that the border is made of elastical sealing material.

According to a further elaboration of the invention it can be provided in a simple way, that no thermostated liquid circulation is maintained as long as no sample support is present and that such a circulation is activated immediately after mounting a sample support by providing that the receptacles have fixing means for the sample support, which fixing means is provided with an actuation member, linked with the valve means to open the same when the fixing means fix the sample support.

A regular flow with which it is attained in a high degree that different cells of the microtiter plate are exposed to equal temperature control conditions, is enhanced when the connection to the compartment is made at the central region of the sample support. Therewith one has preferably a plurality of drains near the border of the sample support. To see to it, therewith, that the air can be driven out of the compartments when maintaining a regular flow, which in an equal measure serves the cells of the compartments, it is according to a further elaboration of the invention provided that there are lower drains joining the bottom of the compartments and upper drains having their opening above the bottom and near to the lower surface of the plate of a related sample support, wherewith it is particularly advantageous if the sample supports tilt slightly in the compartments located below them.

The invention encompasses also a device for feeding a liquid of predetermined temperature to a plurality of connections, which are provided with a valve, which device is provided with a liquid reservoir with a thermostate and a circulation pump. Such a device which advantageously is used as a source for bringing a sample support onto the right temperature, is known from the Dutch Patent Specification NL-C'173 066. The invention aims to simplify such a device and therewith see to it that with simple means at a plurality of connection points thermostated liquid under a suitable pressure and with the right temperature is available. This is attained according to the invention by providing that a circulation duct is located in the reservoir, connected with closable connections and debouches into the reservoir by means of a flow resistance.

With such a device it is important that an easily controllable valve is used which at the one hand closes completely under influence of the pressure of the heating liquid and at the other hand can be controlled with a relatively small force. Accordingly a further elaboration of the invention provides that the valve has a valve member, which at both ends is provided with a sealing means cooperating with a valve seat and is freely located in a sheath and provided with a liquid passage having openings at locations between the sealing means and at the location of a side outlet of the sheath, wherewith the sheath at the end of the one seat is connected to a liquid connection and at the other end cooperates with a control member.

In the following the invention is elucidated on hand of the drawing, in which:

Figure 1 shows a plan view of an embodiment of the invention;

Figure 2 shows a cross-section over the line II-II of fig.1; and

Figure 3 shows a detail.

In fig. 1 reference 1 indicates a reservoir. Above the left side of this reservoir six receptacles 2 have been applied and above the smaller right side a plate 3 is present with an intermediate wall 4 suspending downwardly, which, however, does not reach the bottom 5 (see fig. 2) of the reservoir. In the left part of the reservoir a plate 7 lies on two support beams 6, which plate tilts upwardly from the sides towards the centre with an angle of about 15°.

On this plate 7 six cushions 8 are mounted, which serve as a base for receptacles. In the centre of these cushions a hole 9 have been applied through which a pipe 10 passes, which also goes through plate 7. Via a hose 11 the tube 10 is connected to the output of a valve 13, which by means of a feeding tube 14 is connected to a main duct 15 which is located below the liquid level 16 in the reservoir 1. As has been indicated with interrupted lines in fig. 1, the main duct 15 is U-shaped and has a feed 17 from a pump and thermostatic controlled temperature adjustment or thermostate device 18, which may be of a type known per se. At the ends of the U-shaped tube 15 flow resistances 19 have been mounted.

In the plate 7 props 20 are mounted, which in a manner known per se are height adjustable and bear pivots 21 for clamp braces 22.

Each cushion 8 of elastic material, preferably elastomeric foam material with closed cells, is provided with drains 23 located at the lower side of each cushion and 24 at the higher side. The drains 24 have upwardly emerging small tubes, so that their mouths are located above the surface of the cushion 8.

On each cushion a microtiter plate 25 is laid, which, when pressed down, with its edge 26 seals on the related cushion 8.

On each microtiter plate 25 a cover 27 is located, which with its edge 28 is pressed against the border 26 of the microtiter plate.

The brace 22 is mounted somewhat eccentrically on pivots 21, by reason of which it passes a dead point when turning on these pivots and consequently fixes the microtiter plate 25 and the cover 27 with a snap.

With one of the two braces for each microtiter plate a handle 29 is connected, which can work on a control pin 30' of a valve 13.

As appears more specifically from fig. 2 the pin 30' of the valve 13 is fixedly connected to a valve member 30, having closed end surfaces 31 and 32 and there between a central bore, which by means of each time four holes 34,35 and 36 is connected to the outside of the valve member 30. At the lower side of the valve member 30 an O-ring 37 is

mounted and at the upper side an O-ring 38, which can cooperate with a seat 39 and 40 respectively.

Normally the O-ring 37 engages the seat 39 under influence of the liquid pressure in the duct 14. If, however, a pressure force is exerted on control pin 30 the valve member 30 moves downwardly and the openings 34 become connected to tube 14, wherewith the openings 35 are connected to the drain 12 and the the openings 36 temporarily to the upper room 41 of the valve. This room 41 is connected to the outside of the sheath 43 via three board radial passages 42, so that in the short period in which the valve member 30 is moving downwardly and liquid leaves through the openings 36, this liquid is carried off sidewardly instead of upwardly.

With interruption of the liquid feed the space below the microtiter plate will be aired via opening 36, the upper space 41 and opening 35 via 12, 11 and 10, so that the liquid can easily drain away.

The shown valve has the advantage, that when the counter pressure of the liquid has been overcome practically no more resistance force is encountered, so that some type of snapping action is obtained. Moreover the valve member 30 is amply mounted in the opening 44 in the sheath 43, so that no friction will occur.

The invention has the advantage, that when a microtiter plate has been attached to a cushion 8 and the clamps are fixed the feed of the liquid on the right temperature starts immediately, by reason of which the samples, which are located in depressions are submitted to flowing around of thermostated liquid and attain quickly the right temperature.

The invention combines therewith an easy applicability of the microtiter plates in the device with the possibility to shield the samples by means of the covers and to bring them quickly to the desired temperature without occurrence of locally higher temperatures, which could damage microbiological, enzymological and/or immunological processes to be studied or generated.

Though the invention has been depicted on hand of a device in which the liquid in the compartments is pressurized a little, so that the microtiter plates have to be fixed by mechanical means, it also is possible to cause the liquid flow through the compartments by means of suction, so that the sample supports are pressed down on the cushions by reason of sub pressure.

## Claims

1. Device with one or more receptacles (2) adapted to receive a sample support (25) having a plate with a plurality of downwardly directed recesses,

such as a co-called microtiter plate, which device is provided with means for maintaining a heat carrying liquid in a liquid store on a controlled temperature and duct means (14) connected between the store (1) and the receptacles, characterized in that the receptacles and/or the sample support are provided with sealing means to form a sealed compartment between the receptacle and the plate of the sample support and that the duct means contain a connection (10,11,12) from the liquid store (1) to the said compartment and a drain (23,24) from said compartment to the liquid store, at least one of the connections (10,11,12) and the drain being provided with closable valve means (13,30).

2. Device according to claim 1, characterized in that the receptacles (2) have a surface (8) with a border, which forms a seal with an edge (26) of the sample support.

3. Device according to claim 2, characterized in that the border is made of elastical sealing material.

4. Device according to one or more of the preceding claims, characterized in that the receptacles have fixing means (20, 21,22) for the sample support, which fixing means is provided with an actuation member (29), linked with the valve means (13,30) to open the same when the fixing means fix the sample support.

5. Device according to one or more of the preceding claims, characterized in that the connection (12,11,10) is connected to a central region of the receptacle.

6. Device according to one or more of the preceding claims, characterized in that a plurality of drains (23,24) is located near the said border (of 8).

7. Device according to claim 6, in which the compartments are rectangular, characterized in that the drains are located near the corners of the compartments.

8. Device according to claim 6 or 7, characterized in that there are lower drains (23) joining the bottom (8) of the compartments and upper drains (24) having their opening above the bottom (8) and near to the lower surface of the plate of a related sample support.

9. Device according to one or more of the preceding claims, characterized in that the receptacles tilt about 5 to 20°.

10. Device according to claim 8 or 9, characterized in that the upper drains (24) are located at the higher side of the receptacles.

11. Device for feeding a liquid of predetermined temperature to a plurality of connections, which are provided with a valve, which device is provided with a liquid reservoir (1) with a thermostate and a circulation pump (18) characterized

in that a circulation duct (15) is located in the reservoir, connected with closable connections (14,10) and debouches into the reservoir (1) by means of a flow resistance (19).

12. Device according to claim 11, characterized in that the valve has a valve member (30) which at both ends is provided with a sealing means (37,38), cooperating with a valve seat (39,40) and is freely located in a sheath having a side outlet (12) and provided with a liquid passage having openings (34,35,36) at locations between the sealing means and at the location of the side outlet (12) of the sheath, wherewith the sheath at the end of the one seat (39) is connected to a liquid connection (14) and at the other end cooperates with a control member (29).

13. Valve having a valve member (30) which at both ends is provided with a sealing means (37,38), cooperating with a valve seat (39,40) and is freely located in a sheath having a side outlet (12) and provided with a liquid passage having openings (34,35,36) at locations between the sealing means and at the location of the side outlet (12) of the sheath, wherewith the sheath at the end of the one seat (39) is connected to a liquid connection (14) and at the other end cooperates with a control member (29).

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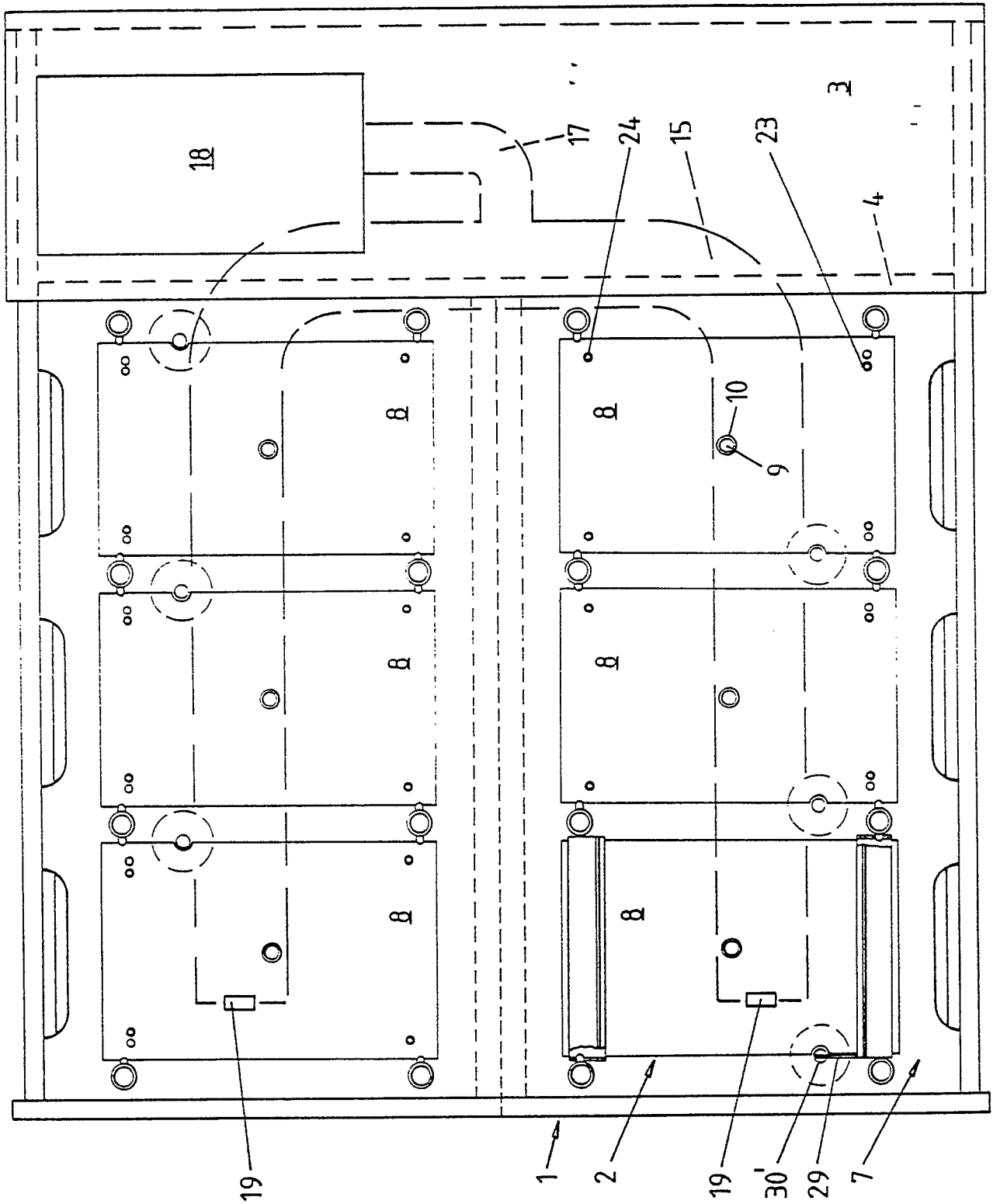
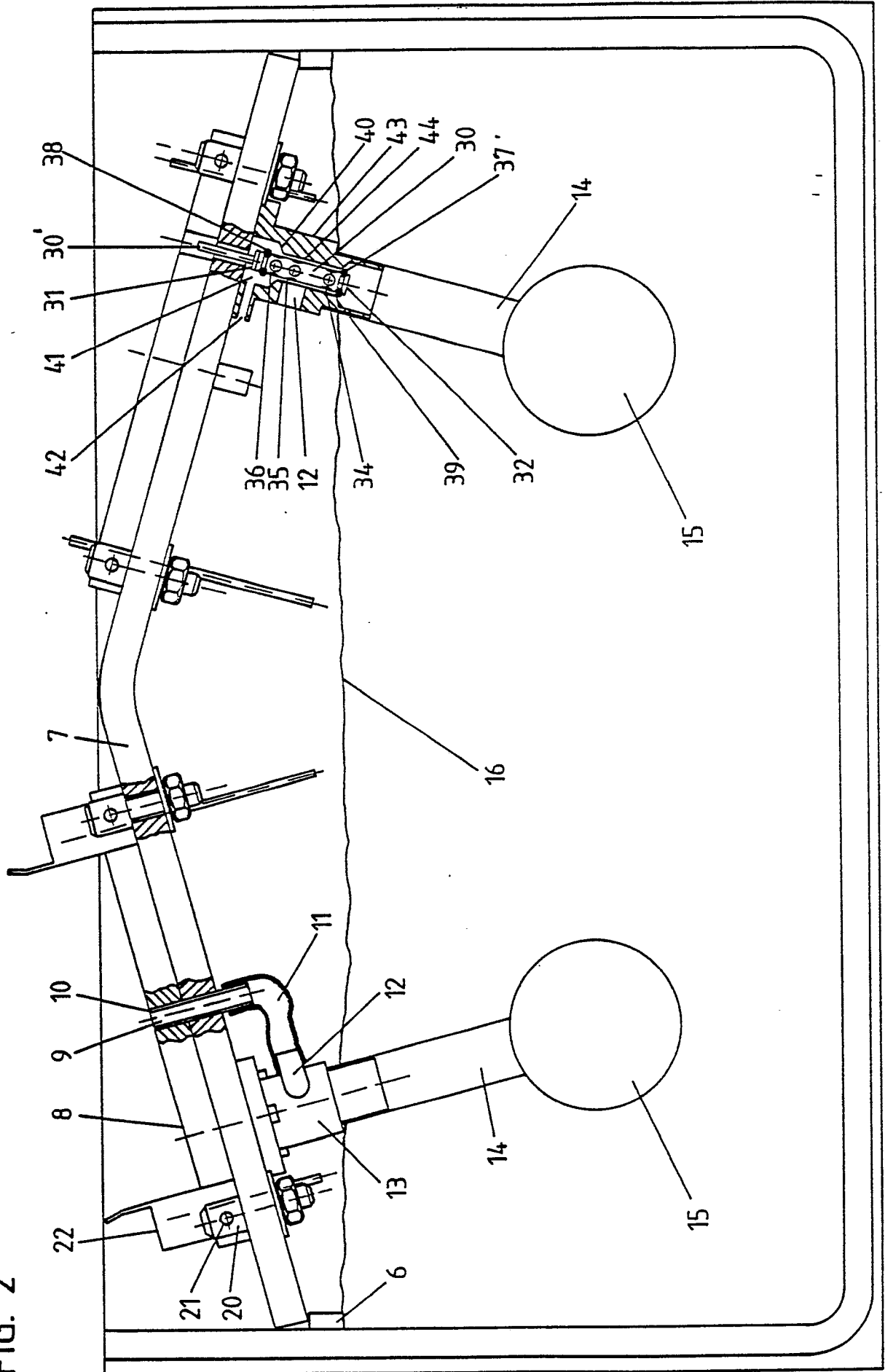


FIG. 1

FIG. 2



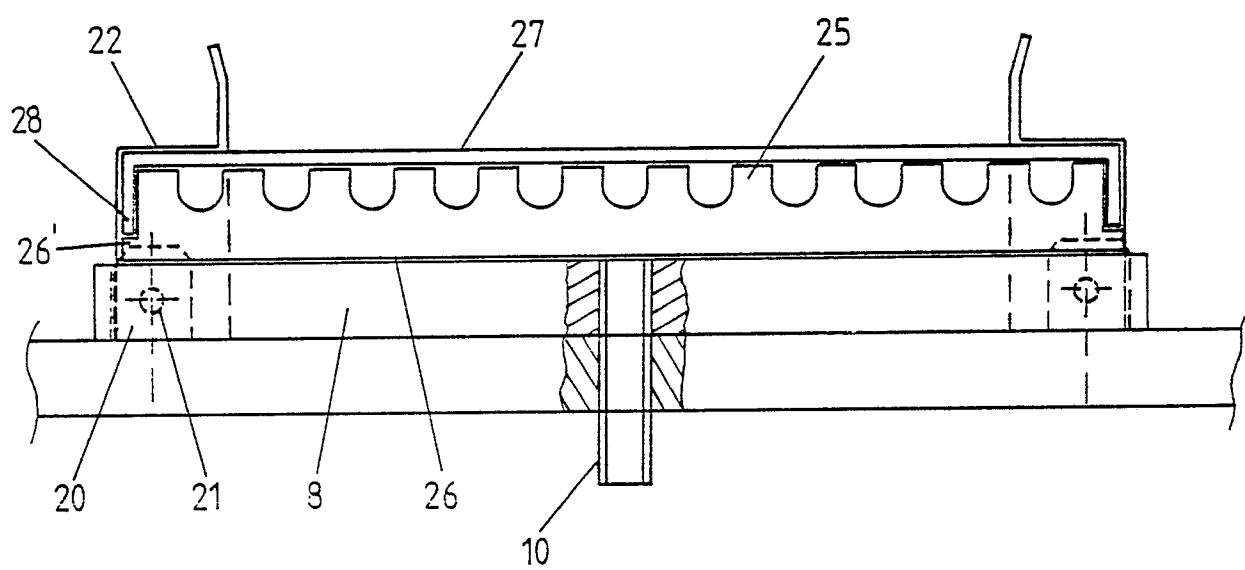


FIG. 3