SCIENTIFIC SECTION

TEMPERATURE REGULATOR.*

BY PAUL S. PITTENGER.

Constant temperature is one of the most important requirements, necessary to obtain accurate results with the various frog, gold fish and isolated uterus biologic assay methods.

In three published papers I described apparatus for automatically controlling and maintaining the temperatures, of water-baths, above or below that of the ordinary room.[1,2,3]

Each of the forms of apparatus described in these papers gave very satisfactory results and was used in our laboratory for several years. During the time they were in operation, however, their limitations were studied with the result that details were noted in which improvements could be made. These improvements are incorporated in the apparatus in use in our laboratory at the present time, descriptions of which follow:

CONSTANT TEMPERATURE-BATH, SPECIALLY DESIGNED FOR FROG AND GOLD FISH EXPERIMENTS FOR MAINTAINING A CONSTANT TEMPERATURE BELOW OR ABOVE THAT OF THE ROOM.

There are many forms of thermo-regulators on the market by which the supply of gas or electricity may be automatically controlled in such a way as to maintain constant temperatures in water-baths, hot air ovens, incubators, etc. Most of these, however, are adapted for maintaining temperatures *above* that of the ordinary laboratory or room.

Biologic assays on frogs and gold fish must be carried out at a temperature of 20° C. For example, the "official" description of the assay for digitalis, strophanthus, and squills contains the following statement:

> "The day before the frogs are to be used, a sufficient number should be taken from the storage tanks and placed in a tank, the temperature of which is approximately 20° C. One hour before the assay, they are weighed to within 0.5 Gm. and placed in wire cages or containers in a tank containing water to a depth of about 1 cm. (1/2 inch), the water being kept at a uniform temperature of 20° C. during the assay."

As the temperature of many laboratories is above 20° C. during the summer months and below 20° C. during the winter, it is necessary, in order to comply with the official requirements, to have some form of apparatus by which it is possible to automatically keep a water-bath at a constant temperature of 20° C. for 24 hours.

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* Scientific Section, A. PH. A., St. Louis meeting, 1927.

1 "A Constant Temperature-Bath for Maintaining Temperatures Lower than That of the Room," by Paul S. Pittenger, JOUR. A. PH. A., 5, 1261 (1916).

2 "An Improved Apparatus for Testing the Activity of Drugs on the Isolated Uterus," by Paul S. Pittenger, JOUR. A. PH. A., 7, 512 (1918).

3 "Temperature Regulator," by Paul S. Pittenger, JOUR. A. PH. A., 11, 338 (1922).

The apparatus described below has been in use in our laboratory for some time and has proven entirely satisfactory.

The complete apparatus is shown in Fig. 1. Figure 2 is a graphic drawing showing the arrangement of the frog cages, thermostat, immersion heater and stirrer within the constant temperature-bath. Also the arrangement of the solenoid valve, ice-water reservoir and method of connecting with circulating ice-water system. The labeling of the corresponding parts is the same in both figures and will serve to illustrate the following description:

Briefly summed up this apparatus consists of a metal tank (*1*) used as a water-bath which is provided with two angle-iron supports (*2*), $^1/_2''$ below the surface of the water, on which the small cages (*3*) for holding the frogs may be placed.

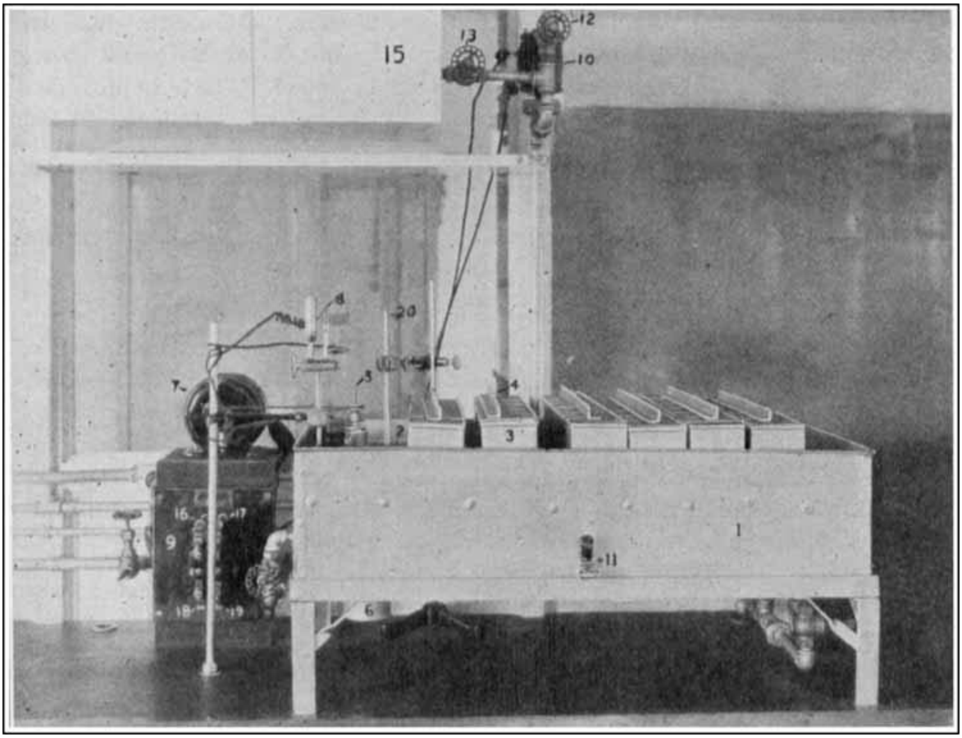

Fig. 1.—Shows the constant temperature-bath, with the individual frog cages in place. Arranged for maintaining constant temperature below that of the room.

In the apparatus shown there are six cages of seven compartments each. For details of the construction of these cages see Fig. 3. Each of the seven compartments of the cage are approximately 3″ x 3″ x 3″. The cages, partitions between the compartments and hinged lids are of galvanized iron while the bottoms of the cages are made of $^1/_4''$ mesh wire screen in order to permit the water to rise to the level of the top of the overflow pipe which is $^1/_2''$ above the angle iron support for the cages. In other words, when the cages are placed on the angle iron support within the tank the water is $^1/_2''$ above the wire screen bottom of the cages. Each cage has seven individual lids the size of the top of each compartment, numbered consecutively. The pieces of angle iron (*4*) are used to prevent the frogs from opening the lids and escaping.

When the tank is used for gold-fish experiments a perforated metal shelf is placed about 3″ below the surface of the water for supporting the beakers containing the solutions of the drug in which the fish are placed.

In the one corner of the tank is a turbine stirring device (*5*) dipping into the water, the bottom end of which extends to the bottom of a reservoir (*6*) which is attached to the bottom of the tank. The turbine stirrer is driven by a motor (*7*) which lifts the water from the bottom of the reservoir to the top of the tank. This keeps the water within the tank in constant circulation and thus maintains an even temperature throughout the bath.

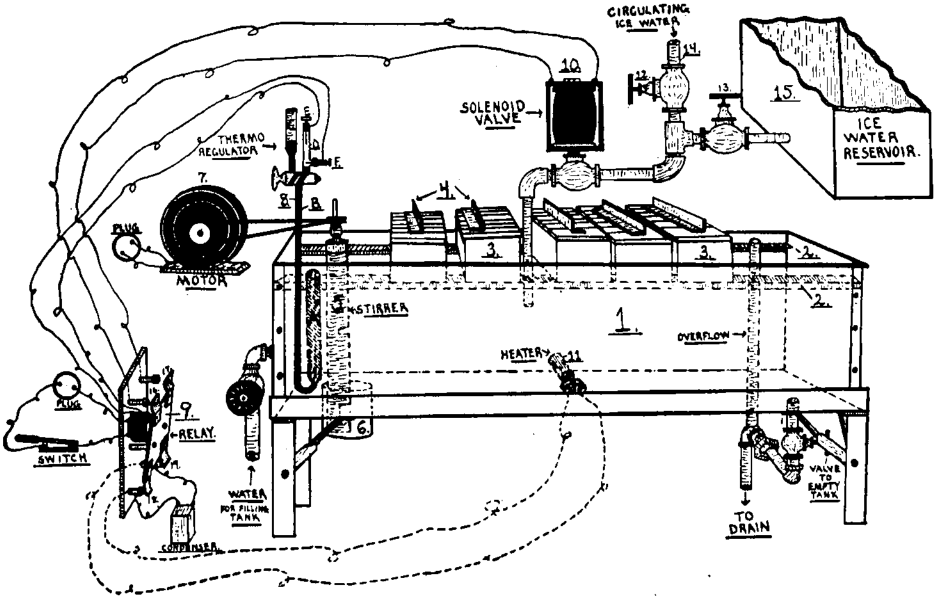

Fig. 2.—Graphic drawing showing the arrangement of the apparatus within the constant temperature-bath and method for connecting the thermo-regulator (*8*) with the relay (*9*) and the solenoid valve (*10*). The dotted lines show the method of connecting the relay with the heater (*11*) when the solenoid valve is disconnected.

In the same end of the tank there is a toluol-mercury thermostat (*8*) which dips into the water and is connected electrically with a relay (*9*). The relay is so arranged that in the summer it may be connected electrically with a solenoid valve (*10*) and in the winter with an electric immersion heater (*11*).

During the summer months when an experiment is to be conducted the toluol-mercury regulator is adjusted to the maximum temperature which we desire to maintain as described later and as soon as the water in the bath rises to this temperature the toluol expands sufficiently to "make" an electrical contact between contact points (*16* and *17*) which are connected with the coil of the solenoid valve (*10*) which releases the ice water, from the ice-water reservoir or circulating ice-water system, and thus the temperature of the water in the tank is lowered.

As the contents of the water-bath become cooler, the toluol in the thermostat contracts and the electrical circuit is broken, thereby automatically shutting off the ice-water supply until the temperature once more rises to the maximum which we desire to maintain.

In our plant we have circulating ice water for drinking purposes which is cooled by an ice machine in the engine room. Through the day while this circulating ice-water system is in operation, we utilize it for cooling the tank and thus avoid the necessity of making and storing ice water for this purpose. At night, however, this circulating system is not in operation and it is, therefore, necessary to provide a means of supplying ice water during this time. This is provided for by the insulated ice-water reservoir (*15*). As the U. S. P. method requires that the frogs be maintained at a constant temperature at least twelve hours before the assay, it is necessary that the temperature of the tank be automatically controlled day and night. By opening the valve (*12*) and closing valve (*13*) the solenoid valve is connected with the circulating ice water through pipe (*14*). By closing

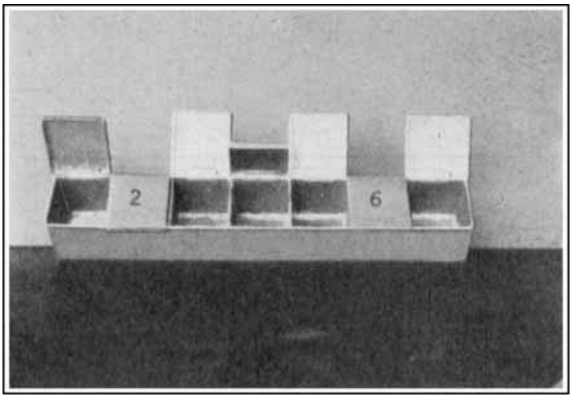

Fig. 3.—Individual frog cages showing the manner in which they are divided into seven compartments with hinged lids and wire-screen bottoms.

Fig. 4.—Cutler-Hammer Solenoid Valve.

valve (*12*) and opening valve (*13*) the solenoid valve is connected with the insulated ice-water reservoir (*15*).

During the winter months the electrical connection between the relay contact points (*16* and *17*) and the solenoid valve is removed and the relay contact points (*18* and *19*) are connected with the electric immersion heater (*11*). After the connections are thus made, as soon as the temperature of the water-bath rises to that at which the regulator was "set" the toluol expands sufficiently to "make" an electrical contact which causes the relay to "break" the current flowing to the electric immersion heater. As the contents of the water-bath become cooler the toluol in the regulator contracts and the electrical circuit to the relay is broken. The relay then automatically "makes" the contact which allows the current to again flow to the immersion heater until the temperature once more rises to the maximum which we desire to maintain.

The construction of the toluol-mercury thermostat is shown in Fig. 2. That portion of the glass tube which is lightly shaded represents toluol (*A*) and the black portion (*B*) represents mercury. In order to adjust the thermostat so that it will throw the relay at 20° C. the two reservoirs *C* and *D* are filled with mercury, the stop-cock placed in the position shown and the bulb (*A*) placed in a water-bath. The temperature of the bath is increased until the surface of the mercury just touches the platinum contact wire *E*. The stop-cock is then turned to the opposite position (connecting *C* and *B*) and the temperature of the bath adjusted to exactly 20° C. At exactly 20° C. the stop-cock is again turned to the original position.

The thermostat will then be adjusted so that the mercury will automatically make the connection between the contacts *E* and *F* thus "making" and "breaking" the circuit flowing to the coil of the relay which in turn automatically "makes" and "breaks" the circuit to the heater. Immediately upon completion of an experiment the stop-cock of the thermostat should be turned so that the reservoir *C* is connected with *B*. As the temperature of the water-bath falls to the room temperature the toluol in bulb *A* contracts and mercury from reservoir *C* passes into *B*. When the apparatus is to be used again the stop-cock is left in this position while the temperature of the tank is being raised to 20° C. As the temperature of the water in the bath increases the toluol expands and forces a portion of the mercury back into the reservoir *C*. The temperature should be carefully watched and at exactly 20° C. the stop-cock again reversed so that reservoir *D* is connected with *B*. The thermostat will then automatically maintain the temperature at 20° C.

The platinum contact point *F*. is connected electrically with the one side of the coil of the electro-magnet of the relay while the contact point *E*. is connected with the one side of the switch, while the other side is connected with the one side of plug *30*. The other side of the plug is connected with the other side of the coil of the relay magnet.

Before connecting the coil of a relay directly with a 110-volt circuit as described above, care should be taken to see that the relay is of the proper type. Many of the stock relays although made to make and break a 110- or 220-volt circuit are equipped with operating coils made to be operated by a 6-volt circuit. A 110-volt circuit would burn out such a relay. With a relay of this type the coil should be connected with a storage battery or transformer.

With a toluol-mercury thermostat as described it is not advisable to pass a 110-volt lighting circuit through the mercury. The relay used in this apparatus, therefore, is a stock Cutler-Hammer Relay No. 232 (with the contacts normally open) which has the coil so constructed that it is satisfactory for continuous duty and may be connected directly to the 110-volt circuit. Although the voltage remains the same, the coil reduces the amperage sufficiently to allow the use of the mercury thermostat.

The relay must be of the type shown in Fig. 2 which has *four contacts* so arranged that two (*16* and *17*) will break a contact when the magnet is active.

In the summer months the solenoid valve is connected with contacts *16* and *17* so that when the mercury in the thermostat closes the circuit to the coil of the relay, the relay will "make" the circuit through these two contacts to the solenoid valve, thus releasing the ice water.

During the winter months the wires between the valve and contacts *16* and *17* are disconnected and wires from contacts *18* and *19* connected. With this "hook-up" when the mercury in the thermostat closes the circuit, the coil of the relay will "break" the circuit to the heater.

As the heater consumes 500 watts a considerable spark is generated at the make and break of the relay unless a condenser is connected with the two contact points. A condenser of a suitable size will absorb the spark and prevent the contact points from pitting and sticking.

CONSTANT TEMPERATURE-BATH, SPECIALLY DESIGNED FOR ISOLATED UTERUS EXPERIMENTS, FOR MAINTAINING A CONSTANT TEMPERATURE ABOVE THAT OF THE ROOM.

The details of the construction of an apparatus for isolated uterus experiments and a device similar to the above for automatically maintaining a constant temperature bath for Pituitary Assays was described by the author in a former paper.[1]

RESEARCH PHARMACOLOGICAL LABORATORIES,
SHARP & DOHME, August 8, 1927.

THE COMPARATIVE PHARMACOLOGIC ACTION OF EPHEDRINE AND ADRENALIN.

BY L. W. ROWE.

Although the active alkaloid ephedrine was first isolated in pure form from the Chinese drug *Ma Huang* by Nagai (1) in 1887 and some of its pharmacological properties reported upon by Miura (2) in the same year, it was not until recently that this alkaloid of *Ephedra vulgaris* has attracted attention from the medical profession. Amatsu and Kubota (3) first revived the study of this alkaloid, in 1918, but the widespread publication of Chen and Schmidt (4, 5, 6) and of Chen (7 to 18) in the past two years has been chiefly responsible for the clinical interest. Other pharmacological articles by Japanese and German workers are those by Fujii (19, 20) and Nagel (21).

Chemically the empirical formula of ephedrine (22, 23, 24) is $C_{10}H_{15}ON$, while that of adrenalin is $C_9H_{13}O_3N$, and structurally ephedrine is $C_6H_5CHOH.CH.CH_3.NH.CH_3$ while adrenalin is $C_6H_3(OH)_2CHOH.CH_2.NH.CH_3$.

The first reports of the practical use of this drug in modern therapeutics have been made recently by Miller (25), by Fetterolf and Sponsler (26), and by Rowntree (27). Later clinical reports have been made by Thomas (28), by MacDermott (29), by Miller (30), by Gaarde and Maytum (31), Jansen and Kreitman (32) and by Leopold and Miller (33). There seems to be no doubt about the drug possessing considerable merit.

However, in the preliminary pharmacological and clinical reports the impression is given that this new drug should very largely supplant adrenalin for two main reasons, the first being its prolonged action and the second its action after oral administration. It is the purpose of this paper to report pharmacological experiments comparing the action of these two drugs in various ways with the belief that these tests will show that there may be a definite place in therapeutics for ephedrine but that it will not replace adrenalin.

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[1] "An Improved Apparatus for Testing the Activity of Drugs on the Isolated Uterus" (Second Paper), by Paul S. Pittenger, Proceedings of The Pennsylvania Pharmaceutical Association, 1927, *American Journal of Pharmacy*, Sept. 1927.