THE LIMITS OF DURATION OF REVERSIBLE CLINICAL DEATH IN SOME HIBERNATING AND NONHIBERNATING ANIMALS AT A BODY TEMPERATURE OF 0°C AND THE POSSIBILITY OF ARTIFICIAL PROLONGATION OF THIS CONDITION

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Thirteen years ago we demonstrated [1] that our method of chilling and reanimation makes it possible to revive a laboratory rat, chilled to a rectal temperature of 0°C in spite of prolonged stoppage of the heart and respiration. This work was devoted to the improvement of methods of reanimation, the study of the duration of clinical death during profound hypothermia, and of the temperature limits, as well as a search for methods of artificially prolonging reversible clinical death.

EXPERIMENTAL AND RESULTS

Method of Chilling and Reanimation

Figure 1 presents a schematic depiction of our method of chilling and reanimation [4]. Chilling was divided into three stages. Down to 15° the animal is chilled by the "closed vessel method," with the only hypothermizing factors being hypoxia and hypercapnia. The nonanesthesized animal is placed in a hermetically sealed vessel at a temperature of 0-5°; as a result of the gas exchange of the organism, carbon dioxide accumulates in the vessel, and the partial pressure of oxygen is lowered. Under these conditions the animal is chilled to a rectal temperature of 15° as a result of the inhibition of thermoregulation. At the second stage, the animal is immersed in a bath with water and ice, and its body temperature is rapidly lowered from 15 to 0°. As soon as the body temperature has been lowered to 10°, there is a total stoppage of respiration, and then of the heart as well; clinical death sets in. If at the following, third stage, the animal, chilled to 0°, is entirely immersed in a solution of propylene glycol or glycerin possessing a temperature less than 0°, the animal can be chilled below the freezing point and brought into a state of complete supercooling.

The first stage in revival is conducted by the joint action of microwave diathermy, localized chiefly in the region around the heart, and artificial respiration by rhythmic insufflation of air through the nasal openings. After heart activity has resumed and the first independent respiratory motions have appeared, at a body temperature of around 15°, the second stage of revival is begun—warming of the body in warm water (40°). At the last stage (not depicted in Fig. 1), the animal is placed in a dark chamber with a temperature of 32°, which is essential on account of the insufficiency of thermoregulation during the first hours or even day after revival.

Figure 2 presents the dynamics of the variation of certain indices during revival with the aid of microwave diathermy. On the right-hand side of the figure is depicted the topography of the temperature variations during warming (recording at 5 min intervals). The heart region is warmed more rapidly (thermocouple in the esophagus at the level of the heart). The abdominal temperature rises somewhat more slowly and lags more and more behind. The same is also evident from the left-hand side of the figure, which shows, in addition, that from the moment of restoration of the blood circulation (vertical dotted line), in an animal revived by warming of the chest cavity (dark marks), the rectal temperature (triangles) begins to rise considerably more rapidly, and the rectal temperature

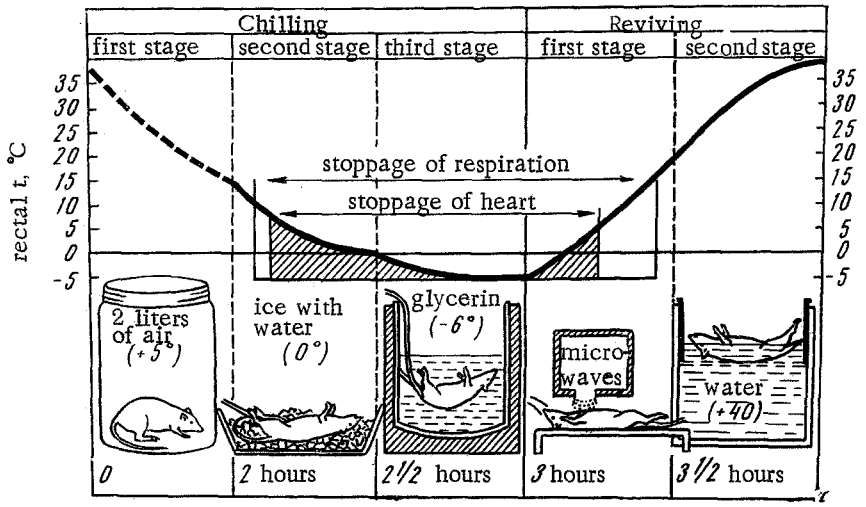

Fig. 1. Scheme of method of chilling and reviving.

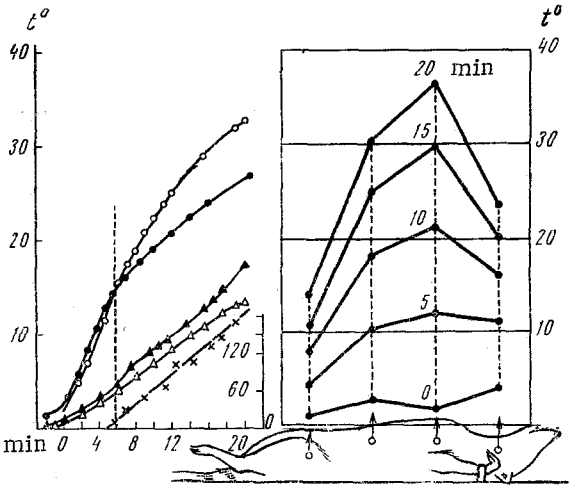

Fig. 2. Influence of local warming by microwave diathermy in the process of revival [3]. Explanations in text.

approaches the temperature of the heart region (circles). This is not observed in a control experiment with warming of the body (white marks). The frequency of the heartbeat in the revived rat is depicted by crosses (with respect to the right-hand ordinate).

Duration of Clinical Death

The permissible limits of reversible clinical death at a body temperature of 0° were investigated in a series of comparative experiments on rats—nonhibernating homeothermal animals—and on gophers (Citellus citellus)—hibernating rodents.

The results of renimation are depicted in Fig. 3. The blackened portion of the column denotes the percent of surviving animals (each column corresponds to a group of ten animals, remaining in the state of clinical death at a body temperature of 0° for a definite time, indicated on the x-axis). The portions of the columns with slanted shading and cross-hatched portions correspond to the percent of animals that die during the first day or two to three days after revival. The unshaded remainder of the column shows the percentage of animals that could not be revived. The data pertaining to the rats show that 100% of the animals can be entirely revived if the period of clinical death does not exceed 60-70 min. Prolongation of this period leads to a lowering of the percentage of entirely revived animals, and this percentage drops to zero in the group of animals that underwent two-hour stoppage of circulation. The results of experiments on gophers indicate that in these animals a considerably longer duration of clinical death can be achieved under the same conditions: 100% of the gophers tolerate three-hour clinical death, while after 5.5 h, 50% of the animals can be entirely revived. Temporary revival is possible in most of the gophers even after seven hours.

The ability to withstand chilling of the body to 0° for a prolonged period is also noted in the golden hamster, although the limits of this tolerance have not been exactly determined. Hence, we believe that the ability to tolerate clinical death for a prolonged period (three hours or more without blood circulation) is a property of hibernating animals. However, it should be emphasized that revival requires artificial reanimation; under natural conditions there is no spontaneous emergence from the state of prolonged clinical death.

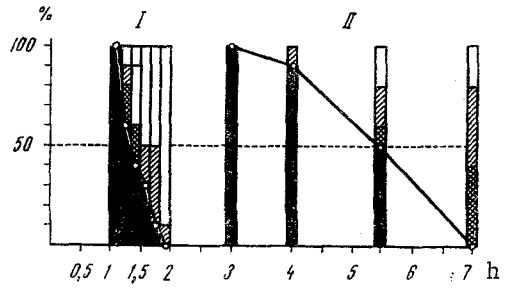

Fig. 3. Revival of rats (I) and gophers (II) as a function of the duration of clinical death at a body temperature of 0°[2]. Explanation in text.

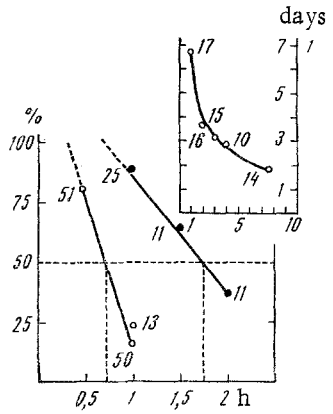

Fig. 4. Revival of white rats before and after "conditioning" (repeated chilling to 0°) as a function of the duration of clinical death. Ordinate) percentage of entirely revived rats; abscissa) duration of clinical death. White circles) control rats (first chilling); black circles "conditioned" rats (after 5-7 preliminary chillings). Numbers next to the circles) number of experimental animals. Upper curve in the corner: time (in days) required for restoration of initial weight after revival (ordinate) as a function of the number of preliminary chillings (abscissa) [2].

Investigating the changes in brain metabolism during clinical death, we began a study of the mechanisms responsible for the tolerance to clinical death of the gopher as a hibernating animal.

Let us emphasize especially that the results that we have reported thus far pertain to gophers that were used in the experiment outside the season of their winter sleep. Our latest experiments with gophers during hibernation show that the physiological changes that occur in connection with the transition of the animals into the state of hibernation do not lead to any increase in the resistance of these animals to clinical death. On the contrary, two experiments (on seven and ten animals) in which the animals were chilled to 0° during the sleeping state at a body temperature of about 10° (series I) or were awakened from hibernation by artificial warming, and were not subjected to chilling to 0°on the following day (series II) indicate a substantial reduction of the percentage of animals surviving after four-hour clinical death at a body temperature of 0°,in comparison with the corresponding group of summer gophers (see Fig. 3). In each series of experiments on animals in a state of hibernation, only one survived.

Hence, although it may be assumed that the greatly increased resistance of the gopher to clinical death is somewhat related to the peculiarities of the state of hibernation, the seasonal physiological changes that make the onset of this state possible do not promote resistance.

Artificial Prolongation of the Period of Reversible Clinical Death

Having established the limits of the duration of clinical death in rabbits and gophers, we attempted to prolong this period experimentally. The only method that gave positive results was repeated preliminary chilling to 0°; moreover, the animals were left each time in the state of clinical death for a definite period. The positive influence of such "conditioning" was demonstrated by our previous, although few, experiments on rats [2]. This time we conducted a series of such experiments on approximately 120 white rats.

Figure 4 presents the results of revival (after a definite period of stoppage of blood circulation at a body temperature of 0°) of control animals chilled for the first time and of rats in which clinical death of a given duration was induced after 5 to 7 preliminary chillings to 0°. The first three times, these animals remained in a state of clinical death for 30 min, and each subsequent time revival was not begun until an hour after stoppage of the heart. The chilling was conducted at 6-day intervals.

As can be seen from Fig. 4, preliminarily "adapted" animals proved more resistant. About one third of these animals tolerated even two-hour clinical death. If we compare the results obtained with data on the duration of clinical death after which 50% of the animals survived, we can conclude that "conditioning" increases the tolerance by 140% (only those animals that were entirely revived were considered in the calculation).

Experiments with "hardening" of gophers by preliminary repeated chillings to 0° (four-hour clinical death each time was alternated with six-day intervals between individual chillings) showed that in these animals the periods of reversible clinical death can also be prolonged by this method. After four preliminary chillings and revivings, the gophers could be entirely revived (five times) even after clinical death lasting seven hours at a body temperature of 0°. This is the longest period of reversible clinical death that we have achieved in animals.

The mechanism of "adaptation," which increases the tolerance to clinical death, is still unknown, and will be the subject of our further investigations. However, we should emphasize that in our experiments on rats preliminary adaptation of the animals to hypoxia, during which they were daily subjected to a lowering of the barometric pressure ("raising" in a pressure chamber to an "altitude" of 8000 meters) did not increase the resistance of the animals to stoppage of blood circulation at a body temperature of 0°. Negative results were also given by preliminary daily (for 15 days) chilling of the animals to 15° without clinical death.

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