SPECIAL ARTICLE

Some Physiopathologic Regularities in the Process of Dying and Resuscitation

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COMPLETE STUDY of the mechanisms of death and resuscitation represents one of the typical trends in the development of modern biology. Investigators were faced with a new class of biological phenomena when the accepted laws and regularities often contradicted the usual concepts of the functions of the living body. A new branch of medical science has come into being, devoted to the physiopathology and treatment of the terminal stages of life.

Investigations pursued at the Laboratory of Resuscitation of the Academy of Medical Sciences of the U.S.S.R. allow certain conclusions to be made on the dynamics of the vital functions during the terminal period and permit recommendation of a definite complex method for the resuscitation of the dying organism. This combination of therapeutic measures consists of transfusion of blood into arteries under pressure in the direction of the heart, artificial respiration, defibrillation with a single condenser discharge and of direct, transthoracic massage of the heart. The choice of the therapeutic method depends on the stage of the terminal period.

Arterial transfusion is one of the leading components of the combined therapy of extreme stages of shock and decompensated blood loss.¹

Stimulation of nerve endings, chemoreceptors and baroreceptors, found in the vascular walls and in the myocardium, with rhythmical arterial blood transfusion represents an essential factor for restoring the activity of the cardiovascular system in cases of severe shock, agony, and clinical death. Arterial blood transfusion also helps to restore the coronary circulation. The blood, to which glucose, epinephrine, and hydrogen peroxide are added, is injected under pressure in the direction of the heart through one of the peripheral arteries; it reaches the aortic bulb and enters the coronary arteries, thus creating a blood flow in the system of the coronary vessels. The myocardium, suffering from extreme hypoxia, receives the lacking nutrition from the blood, oxygen, and glucose, while the epinephrine stimulates cardiac contractions.

Intravenous injection of blood is far from always being effective during the terminal period, and in a number of cases it aggravates the condition partly through marked dilatation of the heart and the possible development of myocardial atony. If intravenous transfusion is administered before agony sets in, and on condition that the arterial blood pressure remains at a level below 60 mm. Hg but for a short time only, such as 15 to 20 minutes, it will be effective. When agonal inspirations begin, intravenous transfusion improves cardiac activity only in some of the cases, while arterial blood transfusion gives good results both in the pre-agonal and agonal periods. It must be stressed, however, that in massive, noncompensated blood loss the effectiveness of intravenous as well as of intraarterial transfusion is directly dependent on the duration of hypotension and the stage of the terminal period. Thus, after 2 hours of hypotension the effectiveness of intravenous transfusion is less in the pre-agonal period and totally absent during agony. After 4 hours of hypotension intravenous blood transfusion in the pre-agonal stage results in a temporary

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increase of cardiac activity. After prolonged hypotension intraarterial blood transfusion is more successful but also has its limits. Thus, after 4 hours of hypotension it gives good results during the pre-agonal period but is of little help during agony; after 5 hours of hypotension, even in the pre-agonal period, arterial blood transfusion gives only temporary improvement.2

Hence it follows that treatment with intraarterial blood transfusion should be started during the early stages of dying. Once the agonal period has set in, even when accompanied with rapid blood loss, intravenous jet injection of large quantities of blood, especially rapid transfusion, is not only useless but is often dangerous. Once the heart is acutely dilated by intravenous blood transfusion subsequent arterial transfusion of blood fails to give any effect. Consequently, if in severe shock or loss of blood intravenous transfusion of 250 to 500 ml. of blood fails to give a sustained rise of arterial blood pressure and fails to improve the cardiac output, intraarterial transfusion of blood must be resorted to immediately.

Yet, the effectiveness of arterial transfusion has its limits. It more often happens that the use of all the components of the combined resuscitation measures becomes necessary; though, in certain cases, for instance, in lethal loss of blood, arterial blood transfusion alone may be effective not only during the terminal period but even after the heart had stopped beating for a short time.

Artificial respiration represents the second indispensable element of the combined method of resuscitation. Artificial respiration should be started as early as possible, preferably simultaneously with the arterial transfusion, for it is essential to affect both the respiration and the cardiovascular system during resuscitation. Artificial respiration with the aid of an apparatus, besides ensuring good pulmonary ventilation, will, through reflex pathways, such as the Hering-Breuer reflex type, stimulate the respiratory center with impulses traveling from the lungs along the vagal fibers to the medullary centers. This stimulation can be effective only if blood circulation has already started in the medulla. The focus of stimulation under these conditions will spread from the medulla to the higher segments and the cortex of both hemispheres. The latter, with the restoration of its functions, provides the most perfect mechanism of controlling the functions of the body. There exists a direct relationship between the time required for the restoration of breathing and that for the restoration of the functions of the central nervous system. The first spontaneous inspiration points to the presence of a focus of stimulation in the medulla. The earlier it appears the earlier will the cerebral cortex return to life and the chance of resuscitation will be better. The interdependence between the degree of circulatory compensation and the possibility of respiratory restoration is seen, for instance, in the fact that such methods, like Laborde's, of neuroreflex influence on the respiratory center on the stimulation of the phrenic nerve by electric current are effective only when the arterial blood pressure is not lower than 80 to 100 mm. Hg. In clinical death the basic method of restoring respiration should be reflex stimulation of the respiratory center by dilatation of the lungs.

As artificial respiration with the aid of apparatus is now widely used, such questions as the composition of the gaseous mixture given to the patient and the analeptics used have acquired special importance. According to our data lobeline, cititone, or carbon dioxide cannot be compared to the reflex method for restoring respiration. Moreover, the deeper the depression to which the respiratory center is subjected the more dangerous is the use of analeptics, as they are capable of only a very brief restoration of respiratory activity and lead to rapid exhaustion and further depression of respiration. At the same time this lessens the possibilities of restoring respiration by other means. Pharmacologic stimulants are indicated only when the corneal reflexes are present and the arterial blood pressure is not below 60 mm. Hg. As to the composition of the gaseous mixture administered to the patient, we believe that the concentration of oxygen must not exceed 30 to 40 per cent. Prolonged administration of pure
oxygen or more than 40 per cent of oxygen during the terminal stage may lead to severe symptoms of hyperoxia. Addition of carbon dioxide (from 1.5 to 27 per cent) and the use of Carbogen (95 per cent oxygen plus 5 per cent carbon dioxide) under these conditions will not improve the situation.3

Cardiac defibrillation is the third element in the combined method of resuscitation. Fibrillation may supervene as a result of myocardial stimulation during hypoxia of any origin, during thoracic operations, during cardiac massage, and other measures for restoration of cardiac activity, during artificial hypothermia, and from electroshock. Pharmacologic defibrillation is giving place in recent years to the more effective electrical defibrillation.4,5 The study of the mechanism of defibrillation has shown that it is conditioned rather by the usual stimulating action of electrical excitation than by the inhibitory action on the heart, as was formerly assumed. Our investigations in this field have shown that the most effective method of stopping fibrillation consists in applying to the heart a single electrical impulse of 0.01 second in duration, which is near to the time of useful myocardial stimulation. A special apparatus generates single electrical impulses in the form of a condenser discharge of a definite capacity (24 microfarads) with the inductance of the circuit of 0.25 henry. Fibrillation can be stopped with the aid of this apparatus either on the exposed heart or with the thorax intact.6 If the fibrillation has lasted for more than 1 to 1½ minutes and also if it has supervened with insufficient or absent circulation or poor pulmonary ventilation, it is necessary to transfuse blood intraarterially or massage the heart directly and administer adequate artificial respiration prior to defibrillation.

Finally, the fourth and extremely important element of the combined therapy is direct, transthoracic massage of the heart. If the arterial transfusion of blood and artificial respiration used during the agonal period give no results and clinical death has supervened, massage of the heart should be started at once. Cardiac massage, for instance, often becomes necessary during anesthesia. Studies of terminal stages caused by overdosage of ether, pentothal sodium, and muscle relaxants were conducted at the laboratory. It was shown that during the early stages of dying with arrest of spontaneous respiration, and while cardiac activity is still retained, the main therapeutic measure consists of artificial respiration. As the cardiac activity weakens and the maximum arterial pressure falls below 60 mm. Hg, artificial respiration should be combined with intraarterial blood transfusion. When the cardiac activity ceases and clinical death occurs, the most effective measure consists in the direct massage of the heart combined with intraarterial blood transfusion and artificial respiration.

During cardiac massage it is essential to maintain the maximum blood pressure above 60 to 70 mm. Hg.7 Our investigations have shown that this is best achieved through rhythmic compressions of the heart and fractional transfusions of aerated blood into the artery with epinephrine or norepinephrine added.

Though the causes of death are numerous, many phenomena accompanying the process of dying are to a great extent common to many types of extinction and restoration of vital functions.

The death of a living organism is the disintegration of its unity, interruption of interrelations of the organs and systems both with each other and the external environment. This discoordination develops first of all through suspension of activity of the higher areas of the central nervous system. As is known, the maximum time the cortical nervous cells can survive after blood circulation has ceased is 3 to 5 minutes. With longer periods, profound, usually irreversible changes take place.

Clinical death cannot be separated from the period of dying that precedes it. Sometimes this period can be so exhausting that the most important systems of the body perish before clinical death sets in. And, on the contrary, if the period of dying was sudden and short, resuscitation is still possible after 6 to 7 minutes from the beginning of clinical death.

It is quite natural that the investigators devoted much attention to the metabolic proc-
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esses occurring during circulatory arrest. Biochemical research in our laboratory was mainly concerned with the oxidative processes in the body and the carbohydrate-phosphorus metabolism in the brain.8,9

Experiments on dogs have shown that at the very beginning of dying from blood loss, for instance, when the compensating mechanisms are still active, no profound metabolic changes take place. Definite changes may be detected only toward the end of the bleeding, when the animal has lost about half the total quantity of blood and the arteriolar pressure has fallen to 20 to 30 mm. Hg. Due to the great loss of blood and a decrease of the blood-flow velocity by almost 40 times, toward the end of bleeding the general consumption of oxygen by the body becomes insufficient and typical signs of hypoxic metabolism appear.

The critical stage, as far as metabolism is concerned, is the terminal stage, i.e., the interval when regular breathing has ceased and the agonal state has not yet developed. Glycolysis, a more primitive form of metabolism begins to prevail in the brain tissue; catabolic phenomena prevail over the processes of synthesis. During agony, when physiologic functions are controlled by the bulbar centers only, a further increase of the glycolytic processes takes place. As a result of accumulation of a great quantity of underoxidized products of metabolism the condition of metabolic acidosis supervenes. Disruption of fat metabolism occurs at the same time. The intensity of glycolysis falls gradually as clinical death sets in. Its low level is incapable either of utilizing the sugar formed with the breakdown of glycogen or of demineralizing the inorganic phosphoric acid. The energy resources of the brain tissue are by now practically exhausted.

During the first minutes following the resumption of cardiac activity after 5 or 6 minutes of clinical death, the metabolic processes undergo no great changes. Two or 3 minutes after the resumption of circulation, aerobic glycolysis in the brain begins. With the resumption of breathing the energy resources of the brain tissue are gradually restored. It is interesting to note that the speed of circulation in the cerebral vessels during this period is considerably lower than in other organs. However, the cerebral tissue utilizes blood oxygen only to a negligible degree. Its return to oxidative metabolism during resuscitation takes place gradually. Only toward the end of the first hour after resuscitation does glycolysis disappear and the oxidative processes increase. At the same time oxygen deficiency of the cerebral tissues still continues, which is proved by the higher-than-normal level of lactic acid. The content of the underoxidized metabolites exceeds the initial level, whereas the alkaline reserves of the blood remain at a low level.

Complete normalization of the carbohydrate-phosphorus metabolism of the brain takes place approximately 72 hours after resuscitation. The hypoxic state continues until the functions of the cortex are more or less restored and the body is able to bring into play more efficient compensatory mechanisms.

As is seen from the above data, the biochemical changes in the cerebral tissue during clinical death are distinguished by their great mobility, the exhaustion of the energy reserves of the cells rapidly takes place, after which the destructive processes become irreversible.

The study of bioelectric phenomena in the cerebral cortex permitted detection of a number of important regularities. According to the electroencephalogram, even within 5 or 6 minutes of clinical death changes take place in the brain that make this period qualitatively heterogeneous. Thus, restoration of the electrical activity of the cortex after a short clinical death (1 to 3 minutes) differs from a prolonged one (4 or 5 minutes) though the average duration of dying is the same (15 minutes). The same phases of electroencephalographic restoration after a clinical death of long duration appear later than after a short clinical death. Besides, during the early stages of resuscitation after 4 or 5 minutes of clinical death there appears a special qualitatively distinctive form of activity in the form of spindle-shaped groups of sinusoidal oscillations, 7 to 14 per second, synchronous over the entire surface of the hemispheres and related to the rhythm of respiration.10
Morphologic investigations have made it possible to determine the character of changes in the brain following clinical death and revealed their evolution depending on the duration of life after hypoxia. The morphologic changes are directly related to the severity and duration of the period of dying and of clinical death.

The development of histopathologic changes in the brains of animals subjected to a 5-minute clinical death as a result of acute hemorrhage proceeds in several stages. Immediately after clinical death following a short dying period (7 to 10 minutes) and 20 to 30 minutes after resuscitation histopathologic changes are insignificant and are manifested as an acute swelling of separate cells. They are more pronounced when the period of dying is longer. Three hours after resuscitation, dispersion of the tigroid is noted. After 15 to 24 hours the intensity of the changes is accentuated: There is total tigrolysis and nuclear hyperchromatosis in a significant part of nerve cells, in some of them karyocytolysis occurs; astrocytes are swollen and drop their ramifications; perivascular edema is visible. Some 36 to 48 hours after resuscitation, certain signs of restoration are observed such as the tigroid again taking on stain. Yet, on the other hand, the pathologic process increases; protoplasma of certain cells becomes vacuolized, others stain darkly and decrease in size. On the seventh and the following days unchanged nerve cells are seen in all parts of the brain, but the changed ones are still plentiful. Of other changes vacuolization of the protoplasm, shrinkage, and karyocytolysis persist the longest. Only toward the thirtieth day of the animal’s life after the experiment, the majority of cells regain their usual appearance. The longer the duration of clinical death or the dying period, the greater is the number of perishing cells and the number of minute areas of destruction in all regions of the brain, particularly in the cortex, in the cornu Ammonis, and in the cerebellum.

The concept of high sensitivity of the central nervous system (especially of its brain cortex) to oxygen deficiency is generally accepted. However, one comes across cases, when in sustained circulatory insufficiency (blood loss, shock, etc.), with the arterial blood pressure level below 70 to 60 mm. Hg, the functions of the cortex of the brain are not significantly affected. Later on, despite restoration of the circulation, death will frequently occur. Here the deciding factor in the mechanism of death, when the replacement of blood comes too late, is cardiovascular insufficiency and insufficiency of the internal organs. Myocardial weakness in this case may prevail and then death occurs in a few hours from hemodynamic disorders or from hepatorenal insufficiency, in which case the organism dies somewhat later. What seems paradoxical is the fact that it is not the brain, the organ most vulnerable and sensitive to anoxia, that becomes the site of the most pronounced histopathologic changes. This, however, does not contradict the proposition of its high sensitivity to hypoxia. This property of the brain becomes manifest only when the whole body is placed in equal conditions of hypoxia, as, for instance, in acute anoxia or acute blood loss. In cases of gradual blood loss, hemorrhagic shock or prolonged hypotension a number of compensatory mechanisms protect the brain for some time from the noxious influence of the fall in blood pressure. Dilatation of the cerebral vessels and the increased utilization of oxygen from the arterial blood belong to this group of protective mechanisms. This concept of the mechanism of death in sustained hypotension dictates the necessity of a corresponding therapy, directed first of all at the normalization of the functions of the internal organs.

The above data and considerations, suggesting that in certain cases it is not the changes in the brain that determine the death of the body after sustained hypotension, do not remove the question of the role of the central mechanisms and the cerebral changes in the pathogenesis of blood loss.

One of the most important and complicated problems with which the investigators of resuscitation are faced, is that of prolonging the duration of clinical death following which it would be possible to obtain complete and stable restoration of the vital functions. In
this connection it seemed most tempting to try to use artificial hypothermia and hibernation with the aim of inhibiting the destructive processes in the living tissues, which develop during the dying period and in clinical death.13–16

Artificial hypothermia (26 to 20°) obtained with the aid of general cooling and pentothal anesthesia enables one to obtain complete and sustained restoration of the vital functions in animals after clinical death has lasted up to 1 hour. With the aid of deep hypothermia (12 to 10°) we obtained recently complete and sustained restoration of the vital functions of the organism in animals after 2 hours' duration of clinical death.

At the same time it was shown that if the terminal state develops in the animals already hibernated or when hibernation is combined with hypothermia, the restoration of the vital functions becomes extremely difficult and, in a number of instances, fails. This may perhaps be explained by the fact that the lytic mixtures depress the nervous mechanisms of cardiovascular control and create an obstacle to the restoration of cardiac activity. The negative effect from the hibernation mixture is probably due to the fact that in the terminal stages, when the central and vegetative nervous systems are deeply inhibited, the lytic mixtures tend to depress them even more, which makes resuscitation extremely difficult.17

What has been said above justifies the conclusion that the leading factor, aiding survival of the higher sectors of the brain during hypoxia, is hypothermia and not hibernation. The latter, under experimental conditions when it was combined with hypothermia, made resuscitation difficult even after short terms of clinical death.

Further study of the physiopathology of death and resuscitation of the body must help to understand better the peculiarities of these extreme stages of life and make their treatment more successful.

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