STUDIES IN RESUSCITATION: I. THE GENERAL CONDITIONS AFFECTING RESUSCITATION, AND THE RESUSCITATION OF THE BLOOD AND OF THE HEART.*

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Contents.

INTRODUCTION.

The work on resuscitation was begun by two of us (S. and G.) more than five years ago, intermitted for a time through external circumstances, and then resumed in conjunction with the third author (P.), who is largely responsible for the preparation of the paper for publication. The original incitement to the work was in part the remarkable results obtained by Kuliabko[1] in the resuscitation of the excised mammalian heart. It was clear at the outset that, if the resuscitation of the heart *in situ* could be accomplished after equally long intervals, the limit up to which the resuscitation of an entire animal could be hoped for must be determined by the power of resistance of organs less tenacious of life and less susceptible of resuscitation than the heart. Our first task, then, was to study the conditions of resuscitation of the heart *in situ,* and the next to fix again, in the light of the results of this study, the limits of possible resuscitation of the least resistant of the systems essential

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[1] Kuliabko, *Arch. f. d. gesam. Physiol.,* 1902, xc, 461.

to life—the central nervous system. Several papers[2] have been published on special portions of our investigations. Our present aim is to give a somewhat general view of the subject, covering all the systems so far studied and embodying new results in the case of those systems already treated of. The results on the central nervous system and on the glands and muscles will be embodied in future papers. Besides the practical purpose of the observations—to contribute something, if possible, to the technique of total resuscitation, which might be useful in the treatment of such accidents as chloroform or coal gas poisoning, drowning and other forms of asphyxia,—we constantly kept in view, particularly in our studies on the resuscitation of individual organs or systems, the possibility that by so treating an organ that its activities are suspended, either wholly or in part, and then watching the gradual or sudden restoration of these activities under the various methods of resuscitation, continued for longer or shorter periods of time, some insight might be gained into the life processes of the organ, and the necessary conditions of its activity. If we knew precisely what had happened to an organ or tissue at the moment when, in consequence of interference with the circulation in it, it had ceased to function, and what happened when, under the influence of the restored blood stream, its function again returned, we should certainly possess a very exact knowledge of the nutritive conditions on which its activity depends. If we knew the difference between an organ whose power of normal function is in abeyance but which is capable of resuscitation, and the same organ, absolutely alike, as it seems to all our ordinary tests, when it has just passed beyond the limit of possible resuscitation, we should not be far from an exact knowledge of the meaning of life.

The experiments of Pictet,[3] to cite only one of the many similar results in the field of general physiology, lend particular emphasis to this point. He found that fish might be frozen solid and afterward recover when thawed out, provided the temperature had not

[2] Guthrie and Stewart, *Science,* 1905, xxi, 887. Stewart, Guthrie, Burns and Pike, *Jour. of Exper. Med.,* 1906, viii, 289. Guthrie, Pike and Stewart, *American Jour. of Physiol.,* 1906, xvii, 344. Guthrie and Pike, *ibid.,* 1907, xviii, 14. Stewart and Pike, *ibid.,* 1907, xix, 328; xx, 61. Stewart, *ibid.,* 1907, xx, 407.

[3] *Arch. des Sciences physiques et naturelles,* 1893, xxx, 293–314.

been reduced lower than —15° C. If, however, the temperature had been reduced to —20° C., the fish would not recover when the temperature was raised again.

A formal definition of resuscitation is by no means easy. The circulation in an animal has been stopped for a time. According to the length of the stoppage, changes more or less serious have occurred in the organs. According to the sensitiveness of the various organs to deprivation of blood, the damage to each has been greater or less. If at any moment the question be asked, whether the body as a whole, or any particular organ is capable of resuscitation, the answer must be that much depends upon the method by which resuscitation is attempted. For example, we not infrequently see that, at a certain stage of anæmia of the head end of an animal, the reëstablishment of the circulation and its long continuance may fail to restore the respiration and the other functions associated with the bulb and the higher parts of the brain, Minute after minute, sometimes even hour after hour, goes by, the heart beating fairly well, the blood circulating steadily, but to all our tests, no ground is being gained. The arterial pressure is too low. If now by artificial means the arterial pressure be raised sufficiently, speedy resuscitation may ensue. In such cases, the animal with the means ordinarily employed would be deemed incapable of resuscitation. In ordinary language, it would be said that its head was dead before the circulation was reëstablished. It is only when, under the influence of the higher pressure, the signs of returning function appear that this verdict is reversed. The resuscitability of the animal in such an instance clearly depends on the perfection of the technique employed to resuscitate it. Ought we to say, in another case where resuscitation had not been accomplished even when, in addition to restoring the circulation the pressure was raised, that the stage had been passed at which restoration was possible and that definitive death had occurred before the renewal of the circulation? Plainly we could not say this, since an improved technique might have led to a successful result.

Another question which may be asked is what constitutes successful resuscitation of a tissue element, an organ or an entire animal? It is easy to reply, a restoration of all the normal condi-

tions, structural and functional. But it is difficult to separate the more from the less important conditions and to say of any given tissue or organ or of the whole animal, at a given period in the resuscitation process, such and so many functions have now been resuscitated to the stage which is absolutely necessary for continued existence, such and so many are still wanting or still below the threshold of effective coöperation with other functions. For example, take the resuscitation of a liver cell. It has a certain structure and certain functions. A period of anæmia of a given duration puts a stop to these functions, alters, it may be, the structure of the cell in a definite way. The circulation is reëstablished, the functions of the cell return, perhaps in a definite order. It is again capable of forming glycogen from dextrose, but perhaps as yet incapable of synthesizing ammonia compounds to urea, or of separating from the blood the constituents of bile. It may perhaps be capable of forming glycogen, but not of performing the converse change of glycogen into dextrose or of producing the ferment by which the latter change is accomplished. Its structure, or what histologists denominate its structure (a more or less artificial picture perhaps) may be restored *pari passu* with the restoration of function, so that it might be possible to say, from a microscopic examination of the cell, at this moment it is capable of forming bile but incapable of forming urea, or the relation between the restoration of function and of structure may be a very complicated one, and extremely difficult to decipher. At what stage shall we say the resuscitation of a hepatic cell is completed? Again, it is very easy to reply, "When it does everything that the normal hepatic cell does in quantity and quality, and when its structure is the same." But again it is, at present, quite impossible, before resuscitation has been attempted, to predict whether, or how completely, it will occur. Take, for example, the resuscitation of a neurone. Undoubtedly the most important criteria of its recovery are that it should again be susceptible of being excited and of conducting the excitation. But we know that there are differences in the resuscitability of different parts of the neurone, the synapse, *e. g.*, being less easily resuscitated than the axone. And it is not easy to say at what precise point the threshold of resistance, whatever it may

be, at the synapse becomes so low that it can be considered normal.

When we take the case of an entire organ, the question is still more complicated. It is not only that the resuscitability of different cells of the organ may be different, that some of the hepatic cells, *e. g.,* having perhaps suffered definitive death while others are still resuscitable, just as certain erythrocytes in a given specimen of blood are always more resistant to the action of a given hæmolytic agent than others, but that the different tissues which compose an organ are, in general, of unequal resuscitability. If a certain proportion of the hepatic cells never recover any functions, and ultimately degenerate and disappear while others perhaps recover certain functions without recovering all, and the rest of the hepatic cells are completely restored, or if the vaso-motor and secretory nerves of the liver (assuming that the latter exist), or some of them, remain, after a given period of anæmia, incapable of resuscitation while the rest recover, by what practical criterion shall be decided the degree of resuscitation of an organ as a whole?

Where the resuscitation of a whole animal is considered, the question becomes still more difficult, for the completeness of the resuscitation of any given organ is inextricably dependent on the completeness of resuscitation of others.

We may, indeed, speak not only of the resuscitation of an organ or a function, but also of the resuscitation of a reaction, even a chemical reaction, in the animal body. And it may even be most philosophical to consider that effective resuscitation of an entire organ has been accomplished when certain fundamental and indispensable reactions are again taking place in proper sequence in time and proper distribution in space in the body. What, for example, has occurred when the respiratory center has once more begun to discharge itself but that certain reactions in abeyance for a time are once more running their normal course in the elements of the center and propagating themselves, or some other reactions which are normally linked with them, along the efferent axones? We say that the respiratory center and its efferent pathway have been resuscitated. What we actually observe is that the spontaneous discharge is again taking place. With what alterations in the so-called structure of its histological elements this discharge may be compatible, we do not at present know.

The possibility that in resuscitation certain chemical reactions of the liver cells may be separately restored has already been mentioned. Many other instances of the possible resuscitation of a reaction without the complete resuscitation of the organs themselves might be alluded to. For instance, it is known that curves representing the rate of oxygen consumption and carbon dioxide excretion in excised muscle subjected to artificial circulation at temperatures below that of the body diverge widely from each other, suggesting that these reactions are to a certain extent independent of each other. In resuscitation it is conceivable that the one might return while the other was still absent, or that the one might be fully resuscitated before the other. If muscle has a heat-producing mechanism separate from a mechanism by which it transforms chemical energy into mechanical work, the two mechanisms might be separately resuscitated. In the liver and other cells synthetic processes might be resuscitated at a different time from degenerative processes. The power of the cells of the intestinal villi of absorbing fatty acids and soaps might be resuscitated earlier or later than the power of synthesizing these substances to neutral fats. In the visual mechanism, the function of perceiving light might be resuscitated at a different time from the function of distinguishing colors. In the resuscitation of the lungs, the function of excreting carbon dioxide, so far as it does not depend on physical diffusion, might be resuscitated at a different time from the function of absorbing oxygen. This might perhaps be tested by clamping the division of the pumonary artery going to one lung for a time and then releasing it, the pulmonary artery to the other lung being now clamped permanently, and the gaseous exchange through the first lung being studied as it recovers from the consequences of the anæmia. In the case of the pancreas, the internal secretion might be resuscitated at a different time from the external secretion, and after a period of anæmia of the pancreas of proper length, an animal might recover one function and not the other—a possible means of testing the hypothesis that the internal secretion is formed by different histological elements (as the islets of Langerhans) from the external.

The differences in the relative resistances of the various organs

and tissues may be examined from another point of view. Eigenmann,[4] as the result of a long and extensive study of the degenerate eyes of the blind, cave-dwelling vertebrates of North America, concludes that the active structures of the eye, such as the retinal elements and the lens, degenerate sooner and more completely than the passive structures, such as the scleral cartilages. It has been shown,[5] also, that the passive structures, *e. g.*, the corneal cuticula, in the eye of a Cuban cave-shrimp are more resistant than the active structures of the dioptric apparatus, which is represented by the merest vestiges of this apparatus as it exists in the normal decapod eye. But of this dioptric apparatus, not all parts have suffered alike. The cone cells, which constitute the refractive apparatus in the decapod eye and cause the formation of an image, have almost totally disappeared, while the retinula cells, concerned with the perception of light and images, are present to about the number of one hundred. It was suggested that the difference in resistance shown by these two groups of cells might be connected in some way with the probable earlier phylogenetic development of the retinular cells. It is obvious that the stoppage of the circulation, resulting in the failure of the oxygen supply to the cells, or the total anæmia of an organ constitutes an adverse influence of marked severity. The question arises, therefore, as to whether or not we can trace a similar general relationship between the activity or passivity of a structure on the one hand, and the relative phylogenetic age of two closely related active structures or functions on the other, and the resistance of these structures or functions to such general necrotic processes as asphyxia or anæmia.

We may take as illustrative examples the following structures or functions. Bone may be regarded as a purely passive structure. So far as our experimental evidence goes, it seems to be almost unaffected by any agents which do not produce irrevocable loss of bodily functions. The tests for the functional activity of connective tissue in general are so ambiguous that we do not consider it profitable to discuss them here, but we have observed no symptoms in our animals which would lead us to believe that these tissues

[4] Eigenmann, The Mark Anniversary Volume, 1903, 167–204.
[5] Pike, *Biological Bulletin*, 1906, xii, 267.

were very much affected. It is commonly stated by surgeons that the epithelial cells of the skin will retain their vitality for one to two weeks, if left *in situ* and kept on ice, after amputation of a limb, and will grow when placed on a skin wound. We have never seen any case of permanent death of the integument of the head in animals subjected to cerebral anæmia. Integument, as well as bone, is a relatively passive structure, but both have other somewhat active structures intimately related to them—the erythroblasts in the bone, and the pilo-motor muscles and sometimes glands in the skin. We do not know to what extent these more active structures might suffer as compared with the inactive bones and skin.

In cerebral anæmia the muscles of the head region suffer less than the nervous system. A muscular contraction may be obtained by striking the muscle at a time when no reflex movement can be elicited in the same region.

Within the nervous system itself, there is a diversity of reactions to anæmia. The cortical centers succumb first and recover last. The respiratory and vaso-motor centers persist much longer and recover earlier, as we have pointed out before. Another example of different degrees of resistance in two closely related structures of about equal activity is found in the inhibitory and accelerator fibers of the heart-vagus nerve. It has previously been pointed out that after division of this nerve, the inhibitory fibers degenerate more rapidly than the accelerators.[6] We have shown that the inhibitory mechanism succumbs to anæmia sooner than the accelerator mechanism. Carlson,[7] in his study of the cardiac nerves in molluscs, found that some of the lower groups of the phylum have no inhibitory cardiac nerves, or at least none that were demonstrable, and suggests that the accelerator nerves to the heart arise earlier phylogenetically than the inhibitory.

There is little doubt that functionally, as well as morphologically, the cortical centers of the brain are of later phylogenetic origin than the centers concerned merely with the maintenance of life. We have shown that an animal may recover, so far as all the lower

[6] Schiff, *Arch. f. d. gesam. Physiol.*, 1878, xviii, 172; Arloing, *Arch. de physiol. norm. et path.*, 1896, Ser. V, viii, 75.

[7] Carlson, *Amer. Jour. of Physiol.*, 1905, xiv, 16.

nervous centers are concerned, but be almost totally lacking in intelligence.

So little attention has been devoted to phylogeny of function that, even if we possessed the necessary data as to the relative resistance of all the functions, we would still be unable to say whether or not they agreed in more than a very general way with the above hypothesis. But as the study of the ontology and phylogeny of structure has made of morphology the rational science which it is to-day, so we may look to the study of the ontogeny and phylogeny of function to give to physiology some of the generalizations of which it so much stands in need. Furthermore, it is completely in accord with modern views of evolution that a cell or an organism should acquire first those functions which are most necessary for life; and it is conceivable that these necessary functions should be the ones to succumb last to injurious influences in general, and the first to recover when the conditions again become favorable to life. To explain the nature of this resistance would again go far toward explaining the life processes in the cell.

PREVIOUS WORK ON RESUSCITATION.

We have reviewed the literature on some of the special phases of the subject in our previous papers, to which the reader is referred for a fuller discussion.

The idea of resuscitation is so old that it seems impossible to trace its origin. The Hebrew and other literatures of the ancient world contain many references to it, often under the guise of a miracle.

Among physiologists, Legallois[8] in 1812 is credited with the first statement of a belief in the possibility of the resuscitation of parts of an animal or even of a whole animal some time after death. But long before the time of Legallois, the experimental foundation of the subject had been laid by Stenson[9] and Swammerdam[10] in the same year. Stenson attributed the paralysis following ligation of the abdominal aorta to an affection of the peripheral nerves and muscles. Haller,[11] in the next century, held a similar view. Stannius,[12] about the middle of the last century, showed that the irritability of the spinal cord was diminished immediately after occlusion of the abdominal aorta. The credit of pointing

[8] Legallois, Oeuvres de Legallois, with notes by M. Pariset, Paris, 1830, i, 131.
[9] Stennonis, N., Elementorum myologiae specimen, etc., Florence, 1667.
[10] Swammerdam, J., Tractatus de respiratione, Ludwig, Batavia, 1667.
[11] Haller, Elementa physiologiae corporis humani, Lausanne, 1762, iv, 544.
[12] Stannius, *Arch. für physiol. Heilkunde,* 1852, xi, 1.

out the fact that the true cause of the paralysis lay in the anæmic changes produced in the spinal cord is almost universally given to Schiffer,[13] although Vulpian[14] had pointed out the same fact several years before. About two hundred years after Stenson described his experiment its true significance became apparent. The nerve cells of the spinal cord were more sensitive to anæmia than the muscles. Spronck,[15] some years later, showed that an animal might regain complete functional use of the spinal cord following total loss of such function during temporary anæmia.

Brown-Sequard[16] decapitated dogs and, after the head had failed to respond to electrical stimulation of the medulla, connected cannulas with the cerebral arteries. The injection of oxygenated blood caused apparently voluntary movements of the muscles of the face and eyes within two or three minutes. Cessation of the artificial circulation was followed by movements of the lower jaw, respiratory movements of the nostrils, and finally by dilation of the pupils as in ordinary death.

We have published in a separate paper[17] experiments showing that the activity of the decapitated head may be maintained for a considerable time after decapitation, by vascular anastomosis and the circulation of entire blood through it. Suitable nutritive conditions are sufficient to maintain a certain degree of activity of the decapitated head, and an unbroken connection with the spinal cord is unnecessary.

There had accumulated then, relatively early in the past century a considerable body of experimental evidence to the effect that certain parts of the nervous system might be restored more or less completely to a functional state after total loss of function if a proper circulation of oxygenated blood was begun in time. It early became apparent also that the central nervous system was more sensitive to anæmia than the muscles. It is self-evident that the length of time which may elapse after the death of an animal within which resuscitation of the whole animal is possible is determined by the resistance or viability of the part most susceptible to adverse influences or necrotic changes. This weakest part would appear to be the central nervous system. It is therefore of practical importance as well as of scientific interest to determine the period after which the central nervous system may be resuscitated *in situ*. Our experiments on this point, together with a partial review of the literature, have been published in a separate paper.[18] The time limit of total anæmia of the central nervous system after which complete resuscitation is possible is probably below twenty minutes. This is about the same limit set by Batelli[19] and by Mayer.[20]

[13] Schiffer, *Cent. f. d. med. Wiss.*, 1869, 579, 593.

[14] Vulpian, Leçons sur le physiologie générale et compareé du system nerveux, Paris, 1866, 451; *Gazette hebdomadaire de méd. et chirurgie*, 1861, viii, 365.

[15] Spronck, *Arch. de physiol., norm. et path.*, 1888, Ser. 4, i, 1.

[16] Brown-Sequard, *Jour. de la physiol. de l'homme et des animaux*, 1858, i, 117.

[17] Guthrie, Pike and Stewart, *loc. cit.*

[18] Stewart, Guthrie, Burns and Pike, *loc. cit.*

[19] Batelli, *Compt. rend. de l'Acad. des Sciences*, 1900, cxxx, 800; *Jour. de physiol. et path. gén.*, 1900, ii, 443.

[20] Mayer, *Mcd. cent.*, 1878, xvi, 579.

Although the early work on resuscitation dealt largely with the central nervous system, the impetus to recent work came largely from the experiments of Kuliabko[21] on the excised heart.

The resuscitation of the heart has been accomplished (1) by massage *in situ* and (2) by perfusion with some artificial or natural circulatory fluid.

Schiff,[22] correctly, and Hake,[23] erroneously, working independently, are credited with having first practiced direct massage of the heart. The method has come into clinical use with more or less indifferent success. The literature on resuscitation of the heart by direct massage up to the year 1902 is given by Boureau.[24] Prus[25] did an extensive series of experiments on the resuscitation of the heart by opening the thorax, employing Wehr's[26] technique, and massage of the heart. He reports freedom from infection and complete recovery in every way after long periods of stoppage of the heart. It should be pointed out, however, that Prus's means of determining the moment at which the heart stopped beating—the moment when the heart beat ceased to affect a mercury manometer is untrustworthy, and the long periods of time after which he reports complete resuscitation should therefore be accepted with considerable caution. The thorax was not opened until a certain time after the heart ceased to affect the manometer, and the exact time of cessation of the beat was not determined by inspection. In the resuscitation of a man two hours after death from suffocation, the heart must certainly have been beating a part of the time during which it was supposed to be stopped. As we have pointed out above, the period of total anæmia after which resuscitation of the central nervous system is possible is very much less than two hours.

The difference between clinical death and true death should be most closely borne in mind in this connection. There are cases recorded in the literature in which the heart has been observed to beat an incredible period after clinical death. Thus Rousseau[27] observed beats of a woman's heart at an autopsy twenty-nine hours after execution. Parrum[28] observed rhythmical contractions of the right auricle of a rabbit's heart fifteen hours after death. Vulpian[29] observed beats in a dog's heart ninety-three and one-half hours after death. Regnard and Loye,[30] in making an autopsy, observed beats of the heart lasting for about an hour after execution. The only certain way of testing whether or not the heart has stopped is by direct inspection. The heart doubtless continues to beat, although never so feebly, for sometimes minutes, perhaps hours, after it ceases

[21] Kuliabko, *loc. cit.*

[22] Schiff, *Arch. f. d. gesam. Physiol.*, 1882, xxviii, 200.

[23] Hake, *Practitioner*, 1874, xii, 241. Cited by Boureau, q. v.

[24] Boureau, *Revue de chirurgie*, 1902, xxvi, 526.

[25] Prus, *Wien. klin. Woch.*, 1900, xiii, 451, 482; *Arch. de méd. expér. et d'anat. path.*, 1901, xiii, 352.

[26] Wehr, *Arch. für. klin. Chirurgie*, 1899, lix, 949.

[27] Rousseau, *Compt. rend. de l'acad. des Sciences de Paris*, 1855, 11. Cited in Richet's Dictionary, iv, 312. q. v.

[28] Parrum, Bibliothek for Laeger, 1858, x, 46.

[29] Vulpian, *Compt. rend. des Séances et Mem. de la Soc. de biol.*, 1858, v, 1.

[30] Regnard and Loye, *Compt. rend. de la Soc. de biol.*, 1887, Ser. 8, iv, 433, 537.

to cause any movement of a mercurial manometer, and the feeble beat may maintain a circulation sufficient to sustain the life of the nervous tissues as well as of the other tissues. We incline to the belief that these facts, generally overlooked clinically and often experimentally, will explain many of the cases of resuscitation at long intervals after clinical death.

Kemp and Gardner[31] have reported a series of experiments on dogs in which they obtained resuscitation after death from chloroform. The method employed was (direct) massage of the heart and artificial respiration. Tracheotomy was not done but O'Dwyer's tubes were introduced through the larynx. The results were good.

Further summaries of the clinical aspects of cardiac massage have been given by Keen[32] and Lenormant.[33]

Since the appearance of Boureau's paper, Sencert[34] has reported a case in which he massaged the heart by introducing the hand through the abdominal wound made in the course of an operation and massaged the heart through the diaphragm. The recovery was complete.

Very recently, Green[35] has described two clinical cases of cardiac massage occurring in his own practice, and cites thirty-eight other cases from the literature. Green used the subdiaphragmatic method of massage, opening the abdomen and palpating the heart through the diaphragm by means of the fingers introduced through the abdominal wound. In one case the diaphragm and pericardium were incised and the heart palpated directly. The subsequent course in the first case was much like that which we have noticed in cats after temporary cerebral anæmia. There were variations in the pulse rate at varying intervals after starting the heart. Spasms soon appeared and continued more or less intermittently until death some twenty hours later. The temperature rose to an alarming degree.

Floresco[36] has reported a method for starting the quiescent heart by electrical stimulation. Two electrodes, insulated from each other, are passed downward along the carotid artery through a wound in the neck to the heart. Stimulation by induced currents caused the heart to beat after fifteen to forty minutes of stoppage (dogs). Here again we must exercise caution in accepting the results, since Floresco also took as the time of stoppage of the heart the moment when it ceased to affect a mercurial manometer. Concerning the possibility of starting the quiet heart by electrical stimulation we shall speak later on in the paper. The method, if practicable, would possess certain advantages over opening the thorax, such as avoidance of the ugly chest wound.

Resuscitation of the heart by perfusion of a suitable medium through the coronary vessels was also first practiced some years before the work of Kuliabko appeared.

Martin[37] is credited with the first perfusion of the mammalian heart through

[31] Kemp and Gardner, *Medical News,* 1903, lxxxiii, 184.

[32] Keen, *Therapeutic Gazette,* 1904, Ser. 3, xx, 217.

[33] Lenormant, *Revue de chirurgie,* 1906, xxxiii, 369.

[34] Sencert, *Jour. de méd. de Paris,* 1905, Ser. 2, lviii, 1080.

[35] Green, *Lancet,* 1906, ii, 1708.

[36] Floresco, *Jour. de physiol. et path. gén.,* 1905, vii, 785, 797.

[37] Martin, *Studies from the Biological Laboratory of the Johns Hopkins University,* 1890, iv, 275.

the coronary arteries. Langendorff[38] and Porter,[39] working independently, modified Martin's method by ligating all branches of the aorta except the coronaries, thus reducing the volume of blood necessary for a perfusion. The perfusion of the human heart was first done by Hedon and Gilis.[40] The earlier literature, together with a discussion of Martin's work is given by Magrath and Kennedy,[41] and by Porter. While it is of great scientific interest to know that a certain tissue may be roused to activity several days after death, yet, manifestly, it can be of no great practical importance in the resuscitation of an entire animal if it transcends the limit of the weakest link in the systemic chain. Herlitzka[42] has tried the effect of intra-venous and intra-arterial injections of Locke's fluid and adrenalin hydrochloride in the resuscitation of dogs after asphyxia. He avoided opening the thorax and introduced a sound through the carotid artery into the aorta. Injection of Locke's fluid to which a small amount of adrenalin had been added was accomplished through the sound, and the heart caused to beat by establishing the coronary circulation. Pressure in the right heart was relieved by withdrawing blood through an ordinary urethral catheter introduced into the right jugular vein. D'Halluin[43] repeated the experiments of Kuliabko, but failed to obtain the brilliant results claimed by the former investigator.

The work of Locke and others on the effect of solutions of inorganic salts upon the heart has been discussed in a separate paper.[44] The practical applications of the intra-venous or intra-arterial injections of the various salt solutions to the general problem of resuscitation will be discussed in a subsequent section.

A third line of work, subsequent to much of that on the nervous system but antedating most of the work on the heart, was a series of attempts to resuscitate an entire animal after accidental death. Goodwyn,[45] in 1788, wrote on the most effectual means of cure of submersion, strangulation and several kinds of noxious airs on living animals. Burgeois,[46] in 1829, and Kay,[47] in 1834, wrote on the physiology, pathology and treatment of asphyxia, including suspended animation in new-born children, and asphyxia from drowning, hanging, wounds of the chest, mechanical obstructions of the air passages, respiration of gases, death from cold, etc. Curry[48] wrote on the means to be employed for recovery from apparent death due to drowning, suffocation and other like causes. Few positive results were obtained.

A committee which was appointed (in 1862) to investigate the subject of suspended animation, reported to the Medico-chirurgical Society of London in 1862.[49]

[38] Langendorff, *Arch. f. d. gesam. Physiol.*, 1895, lxi, 261.
[39] Porter, *Amer. Jour. of Physiol.*, 1898, i, 511.
[40] Hedon and Gilis, *Compt. rend. de la Soc. de Biol.*, 1892, iv, 760.
[41] Magrath and Kennedy, *Jour. of Exper. Med.*, 1897, ii, 31.
[42] Herlitzka, *Arch. ital. de biol.*, 1905, xliv, 93.
[43] D'Halluin, Résurrection du coeur, Lille, 1904.
[44] Guthrie and Pike, *loc. cit.*
[45] Goodwyn, The Connection of Life with Respiration, etc., London, 1788.
[46] Burgeois, *Arch. gén. de méd.*, 1829, xx, 220, 508; xxi, 227.
[47] Kay, The Physiology, Pathology and Treatment of Asphyxia, etc., London, 1834.
[48] Curry, Observations on Apparent Death from Drowning, etc., London, 1815.
[49] *Medico-chirurgical Transactions*, 1862, xiv, 449.

Bailey[50] has reported a case of resuscitation after freezing. Some remarkable resuscitations have been reported by the editor of the *Lancet*.[51]

A fairly complete account of the condition of the visceral organs after the resuscitation of an entire animal is that given by Prus in his two papers.

THE EXPERIMENTAL RESULTS.

The General Conditions Affecting Resuscitation.—In attempting the resuscitation of an animal, we tacitly assume that no organ or system or constituent of the body which is absolutely essential to life, has suffered irreparable injury. It would be hopeless to attempt a permanent resuscitation after the blood had clotted in the head or great vessels or after putrefactive bacteria and other injurious organisms had entered into it in sufficient numbers to be fatal, or after the blood had been destroyed by chemicals or venom or had suffered such spontaneous changes as rendered it incapable of aiding in the resuscitation of the tissues or of nourishing them normally after they were resuscitated.

It is manifestly impossible to tell the exact moment of clotting of the blood within the heart unless the wall of one of the cavities is incised. After incision, the liberation of the kinase from the tissues of the heart will so hasten coagulation that we cannot take the result obtained as the true time of coagulation. The most trustworthy results will, therefore, be those in which the condition of the blood within the heart is stated exactly as it is found on incision of the ventricles. The results of our observations are given in Table I.

The dogs on which the observations were made had been used by students for experiments on the submaxillary gland, including stimulation of the chorda tympani nerve. In some cases a certain amount of dissection was done on the abdomen after death, such as removal of the stomach. The operative procedures had undoubtedly liberated a considerable amount of kinase from the tissues. Although the early occurrence of clots in our subjects is probably favored by the ante-mortem treatment of the animals, the interval during which the blood remained unclotted is greater than the period after cessation of the circulation after which the central

[50] Bailey, *Physician and Surgeon,* 1903, xxv, 502.

[51] Editorial, *Lancet,* 1904, i, 1005.

nervous system can be resuscitated. Intravascular clotting cannot practically be considered a barrier to resuscitation.

TABLE I.

Showing the condition of the blood in the cavities of the heart on incision at varying intervals after death. November, 1904.

Animal.	Manner of Death.	Time After Death at which Heart was Opened.	Condition of Blood in Heart when Incised.
1. Dog.	Asphyxia after ether.	100 min.	Moderately firm clots.
2. Dog.	Heart stopped from ether.	21 "	No clot.
3. Young dog.	Asphyxia after ether.	30 "	No clot.
4. " "	" " "	25 "	No clot.
5. Pup.	" " "	31 "	No clot.
6. Dog.	Haemorrhage and asphyxia.	115 "	Clot.
7. Dog.	Asphyxia after ether.	130 "	Clot.
8. Pup.	Chloroform.	60 "	Clot.
9. Pup.	"	120 "	Clot in right heart; none in left.
10. Dog.	"	36 "	Small clot in right ventricle; none in other cavities.
11. Young dog.	"	40 "	No clot.
12. Dog.	"	50 "	Moderate coagulation in right ventricle; clot in left ventricle.
13. Young dog.	"	49 "	Clot.
14. Dog.	Haemorrhage and asphyxia.	60 "	Clot.
15. Young dog.	Asphyxia after ether.	23 "	No clot.
16. Dog.	Anæsthesia.	176 "	Clot.
17. Dog.	Hæmorrhage and asphyxia.	153 "	Clot.
18. Young dog.	Asphyxia after ether.	40 "	Partial coagulation in right ventricle, but no clot in left ventricle.

Sollman[52] found that clots occurred in the heart cavities in two out of his three dogs within twenty minutes after death, a time somewhat shorter than that at which we found them. The presence of a clot in the ventricle is probably not, in itself, an absolute bar to the resuscitation of the heart. The left heart seldom contains much blood after death, and a clot found in its cavities would not, in general, completely fill them, and thus prevent the inflow of blood into these cavities. And again, the mere presence of clots, acting solely as foreign bodies in the ventricle, would present no great difficulty, as the introduction of sounds and catheters into the cavities of the heart for the measurement of endo-cardial pressure

[52] Sollman, *American Medicine*, 1904, viii, 455.

is a matter of common occurrence. Ante-mortem clots are occasionally found within the heart and do not seriously embarrass its action. In starting the heart by intra-arterial injections of fluid, the injected fluid, as will be pointed out later, does not necessarily enter the heart cavities at first, but goes into the coronary arteries and reaches the cavities of the heart only after passing through these vessels.

Permanent resuscitation of an animal after the formation of clots in the heart, although perhaps not impossible, is scarcely to be hoped for.

The Resuscitation of the Blood.

Since all that is necessary, under normal conditions, for the life of most tissues is a good circulation of normal blood, functional connection with the nervous system being apparently not indispensable, we are very early met by the questions: (1) What are the criteria of blood of sufficiently good quality for resuscitation of the organs? (2) How long does blood stagnating in the vessels after cessation of the circulation, or shed blood preserved under proper conditions, retain the necessary properties? (3) To what extent can blood which has lost some or all of these properties be itself resuscitated? The change which blood ordinarily undergoes in passing through the lungs, kidneys and other organs constitute in a sense a resuscitation of it, and are qualitatively perhaps the same as the change undergone by stagnant blood when it is again caused to circulate. But it is better to restrict the term to resuscitation of blood whose formed elements have suffered a decided loss of function, though not an irreparable one.

It is impossible to give any very definite answer to these questions. If bacteria have appeared in the blood, or if spontaneous laking has occurred, undoubtedly the blood is below the necessary standard, although even then the circulation of it through normal organs may restore it. Blood which has stood for many hours, or even days, in the ice chest may more or less successfully revive the isolated mammalian heart. The deleterious effect of waste products accumulated in the stagnating blood are not very conspicuous, since restoration after simple asphyxia is relatively easy.

It is known[53] that laked blood is harmful to the isolated heart on account of the liberated potassium salts. It is probable that the harmful effect in resuscitation of an entire animal would not be so great since elimination, or perhaps combination of the potassium salts with proteids, would occur. In any case, in the absence of bacteria or of hæmolytic agents like bile salt, laking of blood at ordinary, and even at body, temperature takes place only after a long interval. An example of the spontaneous aseptic laking of dog's blood is given in the following protocol.

February 13, 1905. Blood was run through a sterile cannula from the carotid artery of a dog into a number of sterile glass tubes which were then sealed in the blowpipe flame.

March 15, 1905. All the specimens are now well laked. There is still plenty of clot in all the tubes. The spectrum was that of reduced hæmoglobin. The color was dark purple.

September 1, 1907. Between this and the last date the tubes were repeatedly examined, without revealing any change. Still much clot, the autolytic processes having ceased to affect the fibrin.

The spectrum is still that of reduced hæmoglobin, except in a tube which was slightly broken at one end. Here the color is brown and the spectrum shows a strong band in the red in the position of the methæmoglobin band. One of the other tubes was shown to be free from bacteria.

As the necessary condition for the resuscitation of the solid tissues is a supply of good blood under proper pressure, the necessary condition of the resuscitation of blood is a good circulation of it through a body whose tissues are in a sufficiently normal condition, or, at any rate, through a certain number of indispensable tissues. Since, in an animal which is being resuscitated under ordinary conditions, neither the blood nor the tissues are normal, the question presents itself whether its own previously stagnant blood is the best circulating medium, or whether it might not be improved by the addition of artificial liquids or of blood from a normal animal of the same species. Crile, for instance, has recently revived the operation of transfusion for the treatment of such conditions as coal-gas poisoning. Since here the serious factor is that the hæmoglobin has ceased to act as an oxygen carrier, it is possible that the introduction of a certain amount of hæmoglobin in salt solution, a simpler proceeding than transfusion, might be efficacious. But

[53] Langendorff, *Arch. f. d. gesam. Physiol.*, 1903, xcix, 30.

hæmoglobin from an animal could only be used if it were demonstrated that it did not exert an injurious action from the formation of anti-bodies, for instance.

The time when the blood loses its bactericidal power so that microorganisms may pass into it from the alimentary canal is not devoid of interest in this connection. It is not probable that the epithelium and other defenses of the organism should prove to be the weakest link in the chain and break down within a period less than that after which resuscitation of the central nervous system is possible, although it has been shown that the epithelial cells of the intestine lose their power of absorbing water from serum placed in the lumen for a long time after they have been subjected to anæmia for a period of fifteen to thirty minutes.[54] Nor is it probable that the blood would lose its bactericidal power toward the ordinary bacterial parasites of the colon within the same time. Longcope[55] found that the blood exerts some action against the *Bacillus typhosus* and *Bacillus coli.* In four to six hours after death some of the common organisms of the intestines are to be found in the neighboring tissues unless the cadaver has been put into the refrigerator immediately after death. This period, however, greatly exceeds that within which we may hope for a resuscitation of the central nervous system, and is, therefore, not a consideration of great practical importance. In addition to the loss of its biological properties—the hæmolytic and bactericidal powers —the serum suffers certain physico-chemical changes,[56] even when sealed in sterile tubes, such as changes in the depression of the freezing point, and changes in electrical conductivity, viscosity and coagulation by heat. The significance of these changes as regards the use of the blood by the tissues is not yet apparent, and none of them would occur within the time elapsing after stoppage of the circulation after which resuscitation of the central nervous system could be hoped for.

Cobra and crotalus venom, as is well known, have a violent hæmolytic action, and death results from the changes in the blood. No means of restoring this laked blood to its former physiological

[54] Reid, *Philosophical Transactions of the Royal Society,* B, 1900, cxcii, 240.
[55] Longcope, *University of Penn. Med. Bull.,* 1902, xv, 331.
[56] Buglia, *Archivio di Fisiologia,* 1906, iv, 56.

condition is known, and a suitable fluid, other than blood itself, which might be used for replacing the damaged blood and sustaining the life of the animal until it could form new blood has not been found. Whether transfusion of blood from another animal, allowing the laked blood to escape, would result in recovery is, of course, an open question.

The attempt to resuscitate the blood by transfusion has, of late, been made in some cases of anæmia and in the extreme cachexia of typhoid fever, with only indifferent success. If it be true that a sufficient supply of normal blood is all that is necessary for the life of the tissues, it would seem that, in cases where transfusion was not followed by recovery, the seat of the trouble lay in the cells; that the cells at the time when the transfusion was made, had already lost some of the functions necessary to life. So far as these functions are concerned, the cells might, therefore, be regarded as dead beyond the possibility of resuscitation, and total death would be a matter of a short time only.

The effect of defibrinated blood in maintaining the activity of the heart and some of the secretions is shown in the accompanying protocol. The results are not as good as when fresh blood is circulated through these organs, as we have good experimental reasons for thinking that the cells would have recovered if they had been supplied with fresh blood. The reason for this difference is unknown to us, but we believe that the experiments point toward the conclusion that blood soon undergoes changes which affect even its nutritive, as well as its bactericidal properties.

Experiment of March 1, 1905.—Pup, etherized, was kept in hot box.

11:23 A. M. Tied right subclavian artery and vein. Artificial respiration.

11:26. Tied aorta and put cannula in central end.

11:28. Tied inferior vena cava, after elevating hind end and bandaging abdomen.

11:38. Put cannula in aorta, toward heart, running it up into the auricle. Corneal reflex present.

11:39. Tied heart in auriculo-ventricular groove, omitting great veins, and immediately began artificial circulation with dog's defibrinated blood, obtained the day before and kept in the ice box.

11:48:45. Exposed vago-sympathetic trunks in neck without ligating or dividing them.

12:10 P. M. Auricles and ventricles still beating, but not with same rhythm (right auricle 20 in 17 seconds; right ventricle 20 in 45 seconds).

12:16. Added Locke's fluid to some of the blood (equal volumes) and began injecting it.

12:30. Stimulated right vago-sympathetic. Some slowing of right auricle (left not observed) and distinct after acceleration.

12:33. Put a little ether into the mouth. It seems to excite little secretion, but perhaps some was excited.

12:40. Œsophagus about two inches above auricle is beating, with almost same rhythm as auricle. Not very strong beats, but regular, except that occasionally there is a series of two or three beats more rapid than the rest. This more rapid series is not seen in the auricle.

12:51. Ligature was taken off of heart.

12:51:15. Ventricle began beating.

1:10. Superior vena cava and right auricle beating well. Closing outflow tube in inferior vena cava stops auricular beats at once, but does not affect superior cava beats. Verified many times. A very slight pressure in right auricle is sufficient to stop beats. Stimulated right vago-sympathetic. No stoppage of superior cava or auricular beats, but rather an acceleration.

1:22. Stimulated left vago-sympathetic. Still slight opening of left eye, and apparent retraction of nictitating membrane, but the latter may be due to bulging of the eye. (Both eyes have had marked increase of intra-ocular pressure, progressing since the time when the corneal reflexes disappeared (11:48:45) and have been permanently bulged out to an increasing degree.) Auricle is now beating much faster than the superior vena cava, which is beating strongly. Closing outflow tube stops auricle, but does not affect cava. After releasing tube, auricle beats more strongly than before. Some secretion is running from nose. Stimulated left vago-sympathetic. No effect on heart or superior cava.

1:30. Perhaps some increase in lachrymal secretion.

1:32. No salivary secretion, as shown by drying mouth previously.

1:36. Injected pilocarpine.

1:39. Stimulated left vago-sympathetic. Good retraction of nictitating membrane, without any opening of the eye. Some increase of lachrymal secretion in right eye.

1:53. Increased pressure of injection of blood to quicken flow.

1:57. Œsophagus active to direct stimulation.

1:58. Circulation is twice as rapid as before. Good lachrymal secretion, especially of right eye.

2:04. Stimulated right vago-sympathetic. Retraction of nictitating membrane and opening of eye. Now closed inflow tube, and left everything *in situ*.

3:03. Œsophagus and tongue still respond well to stimulation. Stimulated both vago-sympathetics. No effect on eyes. Skeletal muscles of shoulder excitable to direct, but not to indirect stimulation.

3:17. Started circulation. Right auricle soon beating well.

3:28. Stimulated vago-sympathetics. No effect on eyes. Right auricle beating well. Any pressure on outflow tube stops it. When pressure is relieved it beats more strongly than before. Superior vena cava is not beating, nor left auricle. Much secretion flowing from nose, tinged with blood pigment.

3:42. Tongue still excitable to direct stimulation. (Did not try indirect.) Nictitating membranes are getting œdematous and bulge out. Some liquid is

gathering in mouth and throat, free from hæmoglobin. Tongue getting œdematous.

3:56. Stimulated right vago-sympathetic. No effect on eye. Liquid is coming freely from eye. Liquid also collecting in mouth. Gums wet.

4:08. Stimulated vago-sympathetics. No effect on eyes. Incised cornea in one eye to let the aqueous humor escape. It is somewhat tinged with blood. Vitreous humor also allowed to escape. Some blood seen upon or in it. Stimulation of the vago-sympathetic does not affect the eye any more than it did before. (Pressure was relieved in eye as it was thought possible that it might prevent mechanically any change in the pupil.)

4:20. Tongue still excitable, although swollen. On incision, œdematous fluid escapes from it. Œsophagus excitable. Large hemorrhage in its walls. Shoulder muscles contract on direct stimulation, but not on stimulation of nerves in axilla. Same for pectoral muscles. Hind leg muscles inexcitable to direct stimulation. Stimulation of sciatic nerve produces no effect. Experiment stopped.

Another experiment on the artificial circulation of defibrinated blood, to which peptone had been added, through the head end of an animal is of interest in connection with the formation of anticoagulant bodies in this region. We give the protocol.

Experiment of April 8, 1905.—Small bitch. Ether. Hot box. Artificial respiration. Put a cannula in upper end of thoracic aorta and one in inferior cava. Circulated defibrinated dog's blood (obtained eighteen hours before and kept on ice) from bottle through head end.

11:22 A. M. The circulation was poor from this time. Did not tie off heart, but it was scarcely beating.

11:31:45. Began injection. Pupils not dilated. No eye reflexes, nor any other reflexes.

11:35. Twitching of neck muscles in the wound which was going on when the artificial circulation was begun is stronger. Pupils same as before. Tongue has a poor circulation. Artificial respiration was now stopped as heart was not beating.

11:43. Temperature in thorax 33.5° C. The blood, although stirred as it came out of the venous cannula and always strained before being reinjected, has clotted in the wound and no doubt in the blood vessels also.

11:48:30. Interrupted circulation to get rid of clot.

11:56:30. Started circulation again. Twitching of the neck muscles had all disappeared in the interval. No secretion of saliva.

12:05 P. M. Circulation is now good for the first time.

12:07. Tongue is excitable to direct stimulation but needs strong shocks.

12:10. Drew off a tube of blood (1) from the venous cannula.

12:24. Added about ten grams Witte's peptone in 0.9 per cent. sodium chloride to the blood in the artificial circulation.

12:35. Tongue still responds to strong stimulation.

12:38. Stimulated the vago-sympathetic. No effect on eyes. Direct stimulation of neck muscles causes strong contraction. Similarly with the œsophagus.

12:39. Took off another specimen of blood (2) from venous cannula.

12:51. Stimulation of the accelerantes (annulus of Vieussens and inferior cervical ganglion). No effect on heart. Heart had long since stopped. Direct stimulation of the heart causes a beat each time. Massage causes a series of good beats. Heart soon stopped but massage again started good beats, and so on.

12:55. Drew off another specimen of blood (3) from venous cannula.

After twenty-one hours at room temperature no coagulation appeared in (2) or (3). Slight coagulation in (1). Object of the experiment was to see whether the anti-coagulant action of peptone is developed in this limited circulation, but the blood had obviously been rendered almost incoagulable before the peptone was injected.

The Substitution of Other Fluids for Blood.—The value of the various inorganic solutions as media for maintaining the activity of the mammalian brain and heart, respectively, have been considered in separate papers.[57] None of these fluids will sustain the activity of the brain or higher nerve centers for any length of time, and all are ineffectual in maintaining the normal activity of the heart for more than a brief period. Certain points in the action of these fluids upon other organs or systems, and particularly their efficiency as compared with blood will be presented here.

The effect of these solutions in maintaining the reflexes is shown in the following protocol. It will be noted that the results are less satisfactory than when defibrinated blood is used.

Experiment of February 27, 1905.—Large male cat. Ether. Kept in hot box to prevent cooling.

2:05 P. M. Put cannula in central end of right carotid artery and bled animal.

2:10. Finished bleeding. Drew off about 50 c.c. of blood. Defibrinated it and mixed one part of blood with eight parts of Locke's solution. Maintained artificial respiration.

2:38:30. Ligated aorta.

2:42:30. Ligated inferior vena cava, after elevating hind end, squeezing and bandaging abdomen. The heart, which after ligation of the aorta had been beating rather feebly, was at once strengthened. Ligated right and left subclavian veins and arteries.

2:58. Slight light reflex in left pupil. Fair corneal reflex.

2:59. Interrupted circulation by ligatures under innominate and left subclavian arteries. Corneal reflex disappeared in 20 seconds, lid reflex in 45 seconds.

3:01:15. Still strong spontaneous respiratory movements.

3:01:45. No longer any spontaneous respiratory movements.

3:02. Pupils widely dilated. No light reflex.

3:06. Removed ligatures from innominate and left subclavian arteries.

3:08. Strong spontaneous rhythmical respiratory movements. Began injec-

[57] Guthrie, Pike and Stewart, *loc. cit.* Guthrie and Pike, *loc. cit.*

tion of blood mixture into central end of aorta, but injection failed because of a clot in the aortic cannula; removed clot.

3:10:30. Began injection of blood mixture.

3:11. Heart stopped. Kept up circulation by heart massage.

3:15. Stopped injection.

3:20. No return of eye reflexes as yet.

3:28. It was now seen that the left carotid had been included in ligature about left subclavian, and no blood had been passing through it since 2:51 P. M.

3:29. Stopped massage of heart.

3:31. No light reflex. Released left carotid from ligature.

3:32. Began massage of heart again, and injection of blood mixture.

3:36. Stimulated left vago-sympathetic; perhaps slight opening of eye.

3:38. Stimulated left vago-sympathetic. Undoubtedly some openeing of eye.

3:40. Stimulated vago-sympathetic. Some opening of eye.

3:45. Started massage of heart after an interval of four minutes. Added adrenalin to blood mixture and began injecting it.

3:48. Stimulated left vago-sympathetic. No effect on eye. It is now much easier to maintain good blood pressure than before the adrenalin was added. Very slight and slow massage of the heart suffices. The heart even gives feeble beats, although it has been quite motionless before. Beats seem to be synchronous with artificial respiration.

3:52. Stimulated left vago-sympathetic. No change in eye. Œsophagus contracts strongly during stimulation. (The nerve was tied but not divided, and was stimulated central to the ligature.) Neck muscles now excitable.

4:08. Stimulation of vago-sympathetics gives no effect on eye on either side. Direct stimulation of eyelids causes them to contract strongly. Good secretion of saliva seems to be going on. Tongue excitable. No trace of rigor in head end of animal. Stimulation of axillary nerves on left side causes strong contractions of muscles of fore-limb. Did not try on right side.

4:15. Stimulated cortex cerebri on left side. No movements of fore-limbs nor any eye movements. No change in pupils. Pushed electrodes down one and one-half centimeters into the brain (to strike fibers of corona radiata). No effect of stimulation. Even strongest currents produced no effects. Stimulation of axillary nerves is now ineffective on both right and left sides.

Artificial Respiration.—Another necessary condition for the life of the tissues is a sufficient supply of oxygen. Inasmuch as an animal apparently dead is incapable of oxygenating its own blood, some form of artificial respiration becomes necessary.

Artificial respiration by manipulation of the thorax has proved of little value in any serious accident with the anæsthetic. In general, if ether is the anæsthetic used, one may usually resuscitate an animal, a dog, for example, if the thoracic manipulation is begun immediately after the last gasp but before the heart has ceased to beat, and continued at about the normal respiratory rate until spontaneous respiration is again established. Owing to the laxity of

the pectoral muscles, movement of the fore-legs, alternately drawing them up above the head and pressing them downwards against the ribs is useless in a serious case. Sudden, firm pressure applied to the sternum and to the ribs on either side so as to bend the ribs and costal cartilages well in, and a sudden release has proved more efficient in our experiments. An objection to this method is that it often results in injury to the lungs from too violent compression of the thorax. Rhythmical inflation of the lungs by means of a pump or by compressed air is the most effective method we have tried. Care should be taken not to inflate the lungs too strongly, as the increased resistance caused thereby in the pulmonary vessels may be sufficient to stop a feebly beating heart, or rupture of the pulmonary alveoli may occur. Our technique for artificial respiration was given in our first paper[58] on resuscitation, and we will not, therefore, go into further details here.

In certain experiments on the cardiac nerves in which it was necessary to keep up artificial respiration because of opening the thoracic cavity, we observed that ether might be administered long after the respiratory movements had ceased without seriously affecting the heart. The tissues became cyanotic and the blood pressure fell very low, but on discontinuing the use of the anæsthetic, the heart recovered as soon as the blood became well oxygenated.

The possibility of affecting the heart directly, or even of starting beats, by artificial respiration is shown in the protocol, just quoted, of the experiment of February 27, 1905, in which the beats were apparently synchronous with the artificial inflation of the lungs. We have often found that artificial respiration alone is sufficient to restore to activity a heart almost stopped from ether anæsthesia, and particularly from asphyxia, a considerable time after respiratory movements have ceased. The efficiency of artificial respiration alone in starting a heart almost stopped from asphyxia is still more strikingly shown in the following condensed protocol.

Experiment of March 6, 1905. Young male cat, about two-thirds grown. Ether.

10:24 A. M. Occluded head arteries. Eye reflexes and respiratory movements gone in 20 seconds.

[58] *Jour. of Exper. Med., loc. cit.,* p. 292.

10:25:20. A gasping movement.

10:26:40. Respiratory gasp. These gasps have occurred at intervals (8 in 1 minute and 40 seconds).

10:27:20. Released head arteries. Put a glass tube into the larynx.

10:29. Began artificial respiration. No heart beat perceptible at this time, so that really the interruption of the circulation was total for three minutes and twenty seconds, and must have been almost total for one minute and forty seconds more. Heart soon began to beat well.

10:34:10. No reflexes (corneal or light). No movements of any kind.

10:38:35. A gasp. Pupils, which were widely dilated, are getting narrower. Subsequent recovery rapid.

The Resuscitation of the Heart.

We have studied the resuscitation of the heart more extensively than any other organ or system, with the exception of the central nervous system, and as it is the *sine qua non* in the resuscitation of an entire animal, we will consider it first of all. As it has been found that certain influences and modes of death are more injurious to the heart than others, thus rendering resuscitation of the animal more difficult, we shall consider the various modes of death separately.

The Criteria of Heart Stoppage.—We have already mentioned, in the survey of previous work, that the cessation of the oscillations of a mercurial manometer, or the failure of the carotid or other pulse, is an uncertain means of telling whethor or not the heart has stopped. In our experiments the heart has been exposed freely so that the base was easily visible, but mechanical stimulation of the organ was carefully avoided. The length of time elapsing between the cessation of the external pulse and the complete stoppage of the heart is given under the various modes of causing the death of the animals.

As a rule, the stoppage of the heart is accompanied by a convulsive movement or other outward manifestation on the part of the animal, but that heart stoppage may occur without any such outward sign is shown by the two experiments cited below.

Experiment of May 27, 1905.—Adult male cat. Tube in larynx.

9:09 A. M. Head arteries occluded for 45 minutes. Reestablishment of cerebral circulation. Artificial respiration when necessary.

8:07 P. M. Rectal temperature 38.2° C.

8:21. Cornea rather slack. Pupils about half maximum diameter.

8:28. Pulse 209 in the minute.

9:06. Stimulated the left brachial plexus through skin on that side. Strong tetanus of left forelimb. Pulse 187.

9:28. Stimulated right vagus in continuity. Stops heart at once, and causes maximum dilation of the pupil, bulging of the eye and retraction of the nictitating membrane. Repeated with same result. Muscles of the neck are excitable to direct stimulation. Rectal temperature 38° C.

9:47. Right eye still bulging widely, pupil maximum. Nictitating membrane retracted as before. Pupils and membrane have not come back to normal since stimulation of vagus. (Suggesting that contraction of the pupil to half maximum diameter, previously observed, might not have been due to oculo-motor tone.) Left eye same as before.

9:56. Right eye now bulging less; pupil diminished somewhat, but not to what it was before the stimulation. Nictitating membrane partly protruded, but not as much as before stimulation.

10:15. Heart cannot be felt. Opened chest and found it not beating, not even an auricle moving. There was no convulsion, nor movement of any kind to indicate at what time it stopped. Stimulation of phrenic nerve still causes contraction of the diaphragm.

It might be supposed that, on account of its great length, this was an unusual experiment, and that a similar result would not be obtained under other conditions where the spinal centers were not so profoundly exhausted. That this is not the case is shown by the following experiment, in which heart stoppage occurred within a relatively short time after the release of the head arteries. Both experiments go to show the unreliability of outward signs as an indication of the actual condition of the heart.

Experiment of May 29, 1905.—Adult male cat. Ether. Tube in larynx. Artificial respiration.

2:50 P. M. Occluded head arteries, in usual way.

3:31. Released head arteries.

3:52. Pulse 150. Corneal tension increased. Pupil a little less than maximum.

3:59. Rectal temperature 35° C. Pulse 162.

4:20. Noticed that the heart had stopped. No muscular contractions announced the time at which this occurred. Tried massage through chest, but although the heart was felt slipping up and down between the fingers, it could not be started. The pupils became narrower however. Opened chest, and found the heart quite motionless.

After Death from Asphyxia, Drowning, Etc.—We have studied the resuscitation of this form of death more in detail than other forms, and we will therefore consider it in detail, reserving for subsequent sections only the more important differences, the technique

employed and the results obtained in resuscitation after other forms of death. In general, we may say that resuscitation appears to be easier after asphyxiation than after other modes of death. Hemorrhage and anæsthesia tend to make resuscitation more difficult than after asphyxia alone. In order of increasing difficulty of resuscitation we would rank the forms of death as (1) asphyxia, (2) anæsthesia, (3) hemorrhage, (4) electrocution, by the action of induced currents upon the heart.

In nearly all cases the etherized animals were asphyxiated by clamping the trachea. The blood pressure falls to zero plus the residual pressure, within three to five minutes after the trachea is closed, and no oscillation can be detected in a mercury manometer connected with the carotid. On direct inspection, the auricles, and more particularly the right auricle, may be seen to beat for five to ten minutes or even longer.

In two experiments a piece of sheet rubber was tied firmly over the nose and mouth of the unanæsthetized animal.

Drowning was accomplished by immersing the head of the anæsthetized animal in water.

Hemorrhage was sometimes allowed to occur in case of asphyxia, and invariably rendered resuscitation more difficult than after asphyxia alone.

Resuscitation of the Heart by Direct or Intra-thoracic Massage.—This form of massage, as shown by the increase of blood pressure, and the relative certainty with which the heart is started to beat is more efficient than other forms. The heart may be started ten or fifteen minutes or even longer after cessation of the external pulse. When the aorta is occluded so as to confine the circulating blood to the anterior part of the animal, we have obtained resuscitation of cats as late as forty-four minutes after cessation of the external pulse. Prus reports a case of resuscitation of the heart in a dog after direct massage had been employed for two hours.

Doubtless this form of massage also facilitates the removal of waste products from the heart as it does from the skeletal muscles.

The prompt recovery of the heart as a result of direct massage after clamping the aorta is shown in the following experiment.

Experiment of March 18, 1905, Direct Massage.—Cat. Ether.

11:28 A. M. Occluded head arteries.

11:40:45. Released head arteries. Gave ether, as animal was apparently conscious. Soon after this animal stopped breathing. Heart could not be felt. There was certainly no circulation in the brain for from 15 to 20 minutes, and no respiration, in addition to partial anæmia during occlusion. Opened chest, clamped aorta and started artificial respiration.

12:05. Heart started again by massage. Artificial respiration kept up. Heart massage continued at intervals when heart needed it, compression of ventricles being made at the moment when they were felt to be beginning their contraction. Soon massage was unnecessary.

12:20. Pupils still at maximum dilation, eyes wide open; no light reflex. Heart beating well.

12:25. Tears are being secreted, and pupils are somewhat less. Left room.

12:43. On returning cat found gasping. Pupils distinctly less.

A modified form of intra-thoracic massage consisted in producing rhythmical changes of pressure within the pericardial sac. A wide cannula was tied into a small opening in the parietal pericardium, connected with a pressure bottle or a rubber syringe, the whole being filled with salt solution or warm olive oil. By rhythmically raising and lowering the bottle, or compressing the syringe, the intra-pericardial and therefore the endo-cardial, pressure was alternately increased and diminished. It was supposed that this would be less injurious to the heart than long continued massage with the fingers. The results were unsatisfactory.

Efficient as the method of manual massage is, there are obviously two objections: the large chest wound, with the attendant risk of infection, and the danger of actual mechanical injury to the heart. Many attempts have therefore been made to start the heart without recourse to opening the thoracic cavity.

Extra-thoracic Massage.—Rhythmical compression of the thorax over the heart by means of the hands has given fairly good results in certain stages of the heart stoppage; the time when such massage is effective is, however, much too limited to make the method a sure one. Rhythmical compression of the thorax is efficient up to from three to five minutes after the cessation of the external pulse, but it is probable that in every case of successful resuscitation by this method, the heart has not entirely ceased beating. Where we have been sure that the heart has stopped entirely, although for the briefest interval, extra-thoracic massage alone has proved useless.

The degree of efficiency of extra-thoracic massage in favorable cases appears from the subjoined protocol.

Experiment of May 21, 1905.—Cat. Ether. Tube in larynx.

11:59 A. M. Occluded head arteries.

12:40:50. Natural respiration stopped. No gasps after this.

12:05:15. Released head arteries. Heart beating well.

12:08:20. Gasps began.

12:14. No light, lid, corneal or ear reflex. Tube slipped out of larynx. Respiration interrupted for three minutes. At end of that time the pupils were at maximum dilation. Massaged chest. No heart beat can be felt. Cat seems dead.

12:25:20. Heart now felt for the first time. Artificial respiration interrupted until 12:26.

12:26. Artificial respiration was again started. Massage of chest continued uninterruptedly.

12:28. Heart now felt. Beating well.

Often a faithful trial of extra-thoracic massage has failed to start the heart. In nearly all of these cases direct massage has afterward proved effective. We cite one experiment.

Experiment of March 23, 1905.—Large adult male cat. Ether. Tube in larynx. Paralysis of respiratory center from ether. Artificial respiration started without result.

2:18. Heart could not be felt at all. No pulse in carotid (exposed in neck wound). Pupils widely dilated. All reflexes gone. Kept up vigorous massage of the chest for twenty-two minutes, elevating hind end of animal and trying to compress abdominal aorta, with the hand, through the abdominal wall. (Compression tried after massage had been continued for ten minutes without result.) No return of the heart beat occurred. No pulse whatever visible in the carotid. Artificial respiration had been kept up all the time.

2:40. Opened chest, clamped aorta and massaged heart directly. It soon started, but not very strongly. After a little time, the ventricles began to fibrillate while the auricles still beat fairly well.

2:42:30. Pupils have become somewhat smaller.

2:45:30. Heart is beating fairly well, although not so well as in most of the previous similar experiments. The fibrillary contractions are gone. (The abdomen had been opened at the same time that the aorta was clamped, and the intestines, kidneys and other viscera freely manipulated.)

3:08. Heart which had become very poor (*e. g.*, the ventricles beating only once for two auricular beats) was restored by massage and is now beating well.

3:31. First movement seen, viz., twitching of the skin over right shoulder. The twitching is superficial (platysma myoides) as shown by cutting through the muscle and exposing the deeper ones. Later on, the deeper ones began to twitch also.

Rhythmical compression of the thorax of a large dog at a necessary rate for resuscitation is exceedingly laborious and often can

not be kept up for a sufficiently long time. An attempt was made to devise a machine for this purpose. In the development and testing of this Professor J. L. Kessler was associated. Fig. 1 shows the arrangement. Fair results were obtained with this machine, although not so good as results of manual compression, so far as increase in arterial pressure produced before the heart started is concerned. The anticipated advantage of an indefinitely long massage was realized to some extent.

The relative efficiency of manual massage, rhythmical distension of the pericardial sac and mechanical massage will be made sufficiently clear from the following condensed protocol.

Experiment of February 6, 1904.—Young dog weighing ten kilograms. Injection subcutaneously of 10 c.c. of 0.2 per cent. solution of morphia; A. C. E. mixture. Respiration became rapid and shallow, and ceased within about twenty minutes after giving the A. C. E. mixture, and about five minutes after inserting the tracheal cannula. Heart massaged through the chest wall. Respiratory movements soon returned. Stopped massage. Heart beats and respiration soon stopped. No eye reflexes. This procedure was repeated twice.

Now tried mechanical massage with machine. Results were similar to the preceding.

Now opened chest and massaged heart directly. Good carotid pulse obtained. Elevated hind part of animal and connected the carotid with a manometer. A blood pressure of 20 mm. resulted without massage; this pressure was doubled by direct massage, but no pressure above 40 mm. could be obtained by rapid massage. Clamped aorta. Blood pressure now somewhat higher.

Stimulated accelerators on left side with moderately strong tetanizing current from an inductorium. Slow rhythmical beats occurred near the apex of the ventricles lasting about one to two minutes. Close inspection showed no beats and no fibrillary contractions prior to this.

Tried massage with machine. The effect upon blood pressure and pulse was not so good as that obtained by manual massage.

Tied cannula in the pericardium and connected with a syringe filled with water. Rhythmic pressure on the syringe produced only low blood pressure and poor pulse.

Intra-venous and Intra-arterial Injections.—Nothing is more disappointing than the deportment of the heart following injection of 0.9 per cent. sodium chloride or Locke's solution into the carotid artery or jugular vein. The heart remains as immobile as before, or fibrillates a little before going into rigor; the injected fluid slowly but surely distends the right auricle if injected into a vein, and escapes into the peritoneal cavity and also into the lungs, giving rise to pulmonary œdema which would, in itself, prove fatal. But

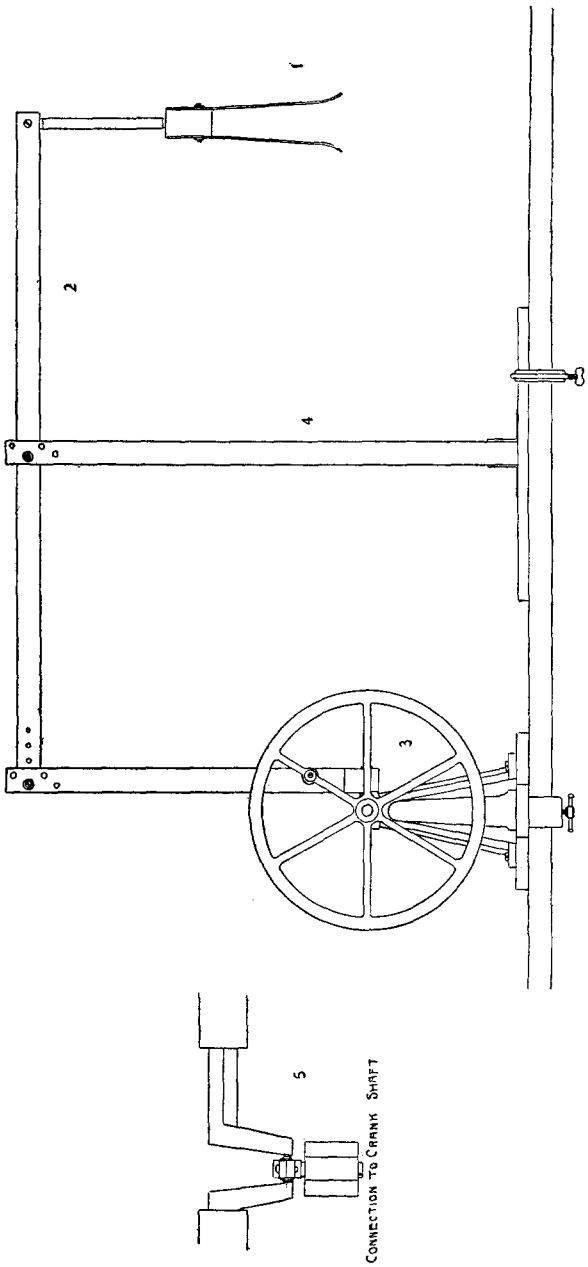

Fig. 1. Showing the arrangement of Professor Kessler's machine. Two sheets of heavy spring brass (1) are bolted to a block and attached to an oscillating beam (2). This, in turn, is attached to a crank shaft (3) revolved by a wheel. A bolt passes through the upright (4) and the beam (2) at their junction. The details of the attachment to the crank shaft are shown in (5). By revolving the wheel, the spring brass sheets are alternately raised and lowered. The animal is placed on a board, the chest covered with towels to protect it from the bruising, and put beneath the brass plates. The rate of compression can be regulated by regulating the speed of revolution of the wheel, and holes in the uprights and in the beam permit of an adjustment of the stroke.

quite apart from the œdema or the occasional rigor produced in the ventricles, the presence in the vessels of such a great quantity of fluid as is usually injected would be likely to overtax the heart, even if it began to beat. Indiscriminate and unconfined injections of fluid are, therefore, worse than useless. This agrees, in general, with Crile's experience.

The suddenness of the onset, and the severity of this œdema, even before the death of the animal, are shown in the following protocol of a typical experiment, in which also some data on the persistence of the reflexes are incorporated, in order to show the effect of artificial fluids in maintaining the activity of the higher centers. In an animal whose heart has stopped from a previous asphyxia, the œdema is even worse.

Experiment of February 20, 1905.—Adult male cat. Ether. Tracheotomy.

2:28 P. M. Put cannula in central end of right carotid, connected with manometer, and began blood pressure tracing.

2:35. Disconnected cannula and drew off 60 to 70 c.c. of blood from the right carotid; then again connected cannula with manometer.

2:50. Tied aorta and put cannula in central end. Bandaged abdomen and elevated posterior end of cat. Kept up artificial respiration.

3:10. Tied inferior vena cava and put cannula in its central end, so as to be able to draw off blood from right heart and restore it to pressure bottle if necessary.

3:12. Tied right subclavian artery and vein.

3:15. Tied left subclavian artery and vein. Corneal reflex still present.

In the interval, the vago-sympathetic trunk was stimulated in the neck, and both central and peripheral effects obtained.

3:33. Began injecting mixture of one part defibrinated cat's blood and ten parts of warmed Locke's solution. Allowed about 10 c.c. to run in.

3:35. Corneal reflex gone. Swallowing movements present. Pupils very much constricted (showing activity of third nerve center). Much liquid (largely saliva?) flowing from nose.

3:48. Swallowed. Heart beating strongly.

Central and peripheral effects of stimulation of vagus, and dilation of pupil on stimulation of sympathetic in neck, obtained several times.

4:06. Began injecting blood mixture.

4:13. Stopped injection. Eyelid reflex back in left eye, but not in right eye. Pupil of left eye less dilated than right (whose carotid artery is tied).

4:15. Lid reflex got in left eye distinctly by touching upper or lower lid. Corneal reflex absent. Secretion still rapidly escaping from nose and mouth.

4:18. Lid reflex increased in left eye, but left pupil is now dilated as widely as right. Pupils soon became insensible to light, although the corneal reflex persists for some minutes.

4:27. Began injecting blood mixture again. Corneal reflex still present, and

persistence of vagus effects, both peripheral and central, although latter gave rise of pressure instead of fall.

4:42. Stopped injection. Artificial respiration stopped to see if any asphyxial rise of blood pressure would occur. No rise of pressure, or very little. No lid reflex in eye.

4:44. Started artificial respiration again. Slight rise of blood pressure.

4:45. Began injecting again. Great rise in blood pressure and increase in force of heart beat.

4:49. Stimulated upper end of right and left vago-sympathetic nerves. The already widely dilated pupils dilated still more.

It was seen that, soon after the recommencement of artificial respiration, intense pulmonary œdema came on, and frothy, bloody liquid rose in the tracheal cannula. The tissues of the neck also seemed rather suddenly to become œdematous. Apparently, the short period of asphyxia had so injured the cells of the capillaries that they became more permeable to the liquids of the blood mixture. There was no trace of œdema in the neck before, and the circulation had never been totally interrupted before the asphyxia.

The Conditions to be Fulfilled in an Intra-arterial Injection.— From a consideration of the conditions necessary for the restoration of the excised heart, we may gain some idea of the conditions which must be fulfilled in order to bring about the restoration of the heart *in situ*. To be efficient, the injected fluid must pass through the coronary arteries, and maintain therein a pressure sufficient to cause contractions of the heart. It is not necessary for the injected fluid to enter the chambers of the heart although it has been shown that the pressure of blood in the chamber will cause some activity of the mammalian heart. The practical problem is to inject the fluid into the aorta in such a way that it shall go through the coronary arteries.

We have accomplished this result by means of a sound near the lower end of which is a distensible rubber sac. The sound is introduced through one of the carotids into the aorta so that the end is between the opening of the innominate and the semilunar valves. The rubber sac is distended by means of a syringe connected with it so as to occlude the aorta above the end of the sound. The injected fluid is then forced into this confined space against the semilunar valves, and through the coronary vessels. The fluid is gradually withdrawn from the distended sac, and the blood allowed to flow past it through the aorta as the heart begins to beat. The sound is finally withdrawn, the heart continuing to beat spontaneously.

The fluids best adapted for injection are defibrinated blood and serum diluted with one to five volumes of 0.9 per cent. sodium chloride solution, and the milk preparation described in a previous paper.[59] There is much less œdema when the blood and its dilutions are used than when the fluids containing the inorganic salts alone, or with the addition of dextrose, are employed for injection.

More recently Herlitzka[60] has accomplished resuscitation of the heart *in situ* in four rabbits by injecting fluid (Locke's solution to which adrenalin chloride was added) into the aorta through a sound introduced into it through the carotid artery. He used no arrangement for blocking the aorta. To reduce the pressure in the right auricle, blood was withdrawn through a urethral cannula introduced into it through the right jugular vein. Under these conditions, Herlitzka says that the path of least resistance lies through the coronary vessels rather than through the systemic circulation, to the right auricle. The heart, as a consequence of the establishment of the coronary circulation, begins to beat.

The necessity of maintaining a suitable blood pressure in order to maintain the activity of the heart *in situ,* even when it has not been previously stopped, or when it has been beating regularly and well for a considerable time after such stoppage has not been sufficiently recognized, and we quote the following experiments as bearing on this point.

The first experiment shows the effect of increasing the blood pressure, without any other remedial agency, on a heart which had rapidly weakened under low blood pressure, and also the beneficial effect of clamping the aorta, thereby increasing the blood pressure, in starting the heart by direct massage.

Experiment of March 20, 1905.—Cat. Ether. Artificial respiration.

3:15 P. M. Head arteries occluded.

3:22:30. Stopped artificial respiration. Natural gasps also stopped.

3:24:45. Again started artificial respiration. Pupils are dilated. Massaged heart (with unopened chest) and kept up artificial respiration. Heart did not start, nor was any sign of life restored, although the massage was vigorous and continued for a long time. Then opened chest and massaged heart directly. Heart did not start. Then clamped thoracic aorta and massaged heart directly.

3:37. Heart started under massage. If massage is intermitted heart stops

[59] *Amer. Jour. of Physiol.,* 1907, xviii, 8.

[60] Herlitzka, *Arch. ital. de biol.,* 1906, xliv, 93.

after a few beats. It is necessary to keep up massage until the heart is beating well (so as to fill the coronary arteries we may suppose). It then went on beating vigorously without an attention. Artificial respiration kept up all along.

4:07:30. First sign of life seen (observations made at very short intervals on eye reflexes, ear reflexes and so forth) namely, slight twitching of tongue and immediately after slight twitching of right corner of mouth. Then immediately a good strong respiratory gasp, involving the shoulders. More movements of the same kind succeed and increase in strength.

4:25. Corneal and lid reflexes back; also light reflex.

4:30. Stimulated left vago-sympathetic. Heart stopped, left eye bulged greatly, pupil dilated. No effect on right eye when left vago-sympathetic was stimulated.

Heart beating well. No doubt the experiment could have been continued, but we wished to see whether, when the aorta was gradually released, the heart would still continue beating.

4:31:30. Partially released clamp on aorta, and then entirely. Elevated hind end of cat.

4:33. Heart is slowing down and weakening. Corneal reflex gone. Pupils markedly dilated.

4:34. Compressed aorta again. Heart at once accelerates and improves in beat.

4:36. Released aorta again. Heart gets weaker. Elevation of hind end has little effect, except that heart fills better.

4:38. Clamped aorta. Heart had almost stopped. Ventricle soon gets stronger, but heart was too exhausted now and experiment was stopped.

The second experiment quoted shows the effect of gradually opening up the abdominal circulation by moving the clamps lower and lower until the splanchnic vessels are reached.

Experiment of March 29, 1905.—Half grown female cat. Ether. Tracheotomy. Artificial respiration. Thorax opened.

1:40:15 P. M. Clamped aorta just above intercostals.

1:41. Clamped head arteries.

2:01. Released head vessels, leaving clamp on aorta. Heart stopped for a beat or two when clamp was taken off of head arteries, but afterwards started up.

2:06. A gasp.

2:06:20. Another gasp. Then respirations go on regularly, five in the minute.

2:08. Respirations six a minute. Both fore limbs, ribs and neck move in the respiration and in fact all the muscles which have circulation. Pupils still dilated to maximum. No eye or ear reflex.

3:18. Strong light reflex. Contraction of pupil.

3:20. Stimulated left phrenic nerve. No contraction of diaphragm. Repeated; same result. Stimulated the diaphragm; fair contraction. Stimulated intercostal muscles; got contraction. Diaphragm does not contract in the natural respiration induced by stopping the artificial. Fore limbs quite excitable reflexly, and extended.

3:25. Stimulated upper end of brachial nerve. Strong reflex contraction

of the opposite fore limb, and of neck on both sides. Stimulation of peripheral end causes strong contraction of the limb.

3:31. Partially released the aorta. Heart soon begins to weaken and slow. Clamped aorta again in thorax; heart improved.

3:35. Clamped abdominal aorta just below the diaphragm above all branches given off below the diaphragm.

3:37. Took clamps off the thoracic aorta. Heart goes on beating as before.

3:38:30. Put clamp on abdominal aorta above the kidneys. Took off upper clamp. Liver is now getting plenty of blood, becoming red at once; also intestines. Heart goes on beating as well as before. Head respiratory movements are going on. Pupils well contracted but no light reflex.

3:43. Slight spasms, after which the pupils are dilated.

3:44. Snapping movements of jaws. Pupils are still widely dilated although not so widely as before. Clamped abdominal aorta above level of the renal vessels.

3:45. Took off upper clamp. The intestinal vessels are widely dilated and filled with blood. Spasms of forelimbs.

3:47. Heart is irregular since last removal of clamp. Now took off the lowest clamp and compressed hind limbs. Heart gets slower and weaker.

3:50. Now clamped thoracic aorta about level of middle intercostals. Heart immediately began to beat more rapidly but soon got slow again.

3:55. Stopped artificial respiration. No spasms. The intestine is not executing any movements. Stimulation of intestines has no effect. The same is true for urinary bladder, which is already strongly contracted and empty, for ureters, Fallopian tubes, and for muscle of abdominal wall.

The slow but certain failure of the heart when the blood pressure is lowered is shown in the third experiment quoted.

Experiment of March 30, 1905.—Cat. Ether. Artificial respiration.

10:48 A. M. Opened chest.

10:52. Clamped head arteries.

10:53. Clamped aorta below origin of left subclavian.

11:17:30. Released head vessels. Heart is beating poorly. Massaged it occasionally. Heart beats poorly, fibrillating a little and requiring occasional massage to keep it going until 11:57 A. M.

11:57. Heart now beating well. The animal continued in good condition, the reflexes returning and the heart continuing strong.

12:44. Corneal reflex back.

12:53. Took clamp off aorta. At once the nose and tongue which have been red become pale and the pupils dilate somewhat, especially the left.

12:55. Light reflex present. Gasping respirations start and now go on regularly, eighteen a minute. The previous apnœa, therefore, was associated with a good blood supply to the head apparently, as the blood pressure must be lower now with the whole animal under circulation after anæmia of the secondary vaso-motor centers in the dorsal and lumbar cord.

1:32. Circulation still going on. Stimulated sciatic. Fair contraction of corresponding hind limb.

1:40. Pupils found widely dilated. Heart stopped some time ago. Massage.

1:42. Heart beating feebly.
1:45. Abandoned experiment.

In none of these experiments could it be objected the heart had not recovered after starting by direct massage, or after the weakening which is such a constant accompaniment of cerebral anæmia. The chemical conditions were undoubtedly good, so far as nutritive value of the blood and its content of inorganic salts and oxygen were concerned. The physical condition of the heart was also good. But neither the blood nor the heart itself was able to overcome the wide effects of disturbing one physical factor in the problem—the blood pressure. This point will be considered again in the portion on the resuscitation of the vaso-motor mechanism.

Injection into Coronary Arteries.—The action of the various fluids on the excised mammalian heart, together with the conditions of its acitvity,[61] has been discussed in another paper. Blood is, of course, the best. Next to this come dilutions of blood with salt solution, the serum and dilutions of serum. Not very far behind serum comes milk prepared as follows: Milk was diluted three or four times with 0.9 per cent. sodium chloride solution after precipitation of the caseinogen with hydrochloric acid and making the filtrate slightly alkaline with sodium carbonate. Solutions of the inorganic salts are far inferior to any of the above. To give the best results, the fluid should, of course, be at the normal temperature of the blood.

The comparative effects of Locke's solution, and of a mixture of blood plus sodium chloride solution, on the same heart at varying times after its excision are shown in the accompanying protocol. It will be noted that, as the interval after death grows longer and the heart ceases to nourish itself well, the fluids become more nearly equal in their ability to elicit beats. It may be that the effects produced by the fluids at this time were purely mechanical, and such as might be produced by perfusion of the heart with mercury, oil or hydrogen gas.[62]

Experiment of February 27, 1905.—Heart of the cat used on February 20 was still in the ice box. On February 20 it had been isolated immediately after it

[61] Guthrie and Pike, *Amer. Jour. of Physiol.*, 1907, xviii, 14.

[62] Magnus, *Arch. für exper. Path. und Phar.*, 1902, xlvii, 200. Sollmann, *Amer. Jour. of Physiol.*, 1906, xv, 121. Guthrie and Pike, *ibid.*, 1907, xviii, 14.

stopped beating and perfused with Locke's solution made with calcium chloride not corrected for water of crystallization. It immediately began to beat and continued beating well. Then stopped perfusion and allowed the heart to cease beating. This it did in less than ten minutes. Then perfused with Locke's solution in which the amount of calcium chloride added had been corrected for water of crystallization. It began to beat at once and continued as well as with the other Locke's solution. No difference could be seen.

Then stopped perfusion and let the heart stop beating. Now perfused with a mixture of one part cat's blood to ten of sodium chloride solution. It beat more strongly than with either of the Locke's solutions. The pressure in all these perfusions was about sixty mm. Hg. in the perfusion bottle and temperature of liquid in the bottle and that of the heart was from 30 to 32° C. Put heart in the ice box. Sixteen hours later took it out and perfused again with Locke's solution under the same conditions of temperature and pressure. At end of about fifteen minutes it began to beat, the ventricles a little below the groove beating more strongly than the auricles. The beats were much feebler than on the previous day. Tried now perfusion with the blood mixture—same mixture as was used the day before. Got the same kind of beats as with Locke's solution. No noticeable difference in strength.

On February 23, forenoon, perfused the heart again with a mixture of cat's blood not perfectly fresh. No beats appeared even after two or three hours.

Put the heart again in the ice chest and kept it there until February 27 forenoon. It had now a slight putrid odor.

February 27, 1 P. M. Perfused it with Locke's solution. No beats whatever could be gotten. Perfusion kept up more than one-half hour.

5 P. M. Perfused heart with a mixture of cat's blood, fresh, and Locke's solution, one part of blood to eight of Locke's solution. No beats could be gotten, not even the feeblest. The same blood mixture causes good beating of fresh isolated heart of the cat obtained one hour after it had stopped beating *in situ.*

The Effect of Adding Drugs to the Injection Fluid.—Adrenalin and suprarenal extract have been injected in resuscitation experiments by a number of workers, probably first by us, and very soon after by Crile. Adrenalin is of slight value in cases where the thoracic aorta is occluded, unless massage is also used. With massage, when employed without occlusion of the thoracic aorta, adrenalin is of considerable value. Care must be taken not to use excessive quantities of the adrenalin, in order to avoid overstimulation of the heart and consequent fibrillary contractions.

We have tried the effect of direct intra-muscular injections of suprarenal extract upon the heart in one experiment.

Experiment of April 19, 1905.—Adult cat. Killed by etherization and bleeding at 4:47 P. M. Heart left *in situ.* Injection of Locke's solution into the aorta beginning at 5:04. The heart was kept beating until 5:22, when emboli were observed in coronary arteries near base of ventricle.

The suprarenal glands of a cat used in a previous experiment on this day were removed and ground in a mortar with Locke's solution.

5:35. Now injected suprarenal extract into the muscle of the ventricles. Strong contractions follow without diastole.

Such a result would manifestly be of no value in an attempt at resuscitation of an entire animal.

The effect of adrenalin when added to the circulating fluid when the heart is beating feebly is shown in the protocol of the experiment of February 27, 1905, cited above. An early experiment on adrenalin shows the uselessness of unconfined injections, even when adrenalin is added, and the impotency of adrenalin chloride itself in starting the heart.

Experiment of November 10, 1902.—Dog of 16 pounds. Given 8 c.c. of 0.2 per cent. morphine sulphate.

3:15 P. M. Anæsthetized with A.C.E. mixture. Tracheotomy.

3:25. Drew off 100 c.c. of blood. Connected manometers with carotid artery and external jugular vein.

3:55. Arterial pressure good. Pressure in right external jugular at base line or negative. Began opening chest.

4:01. Artificial respiration. Stimulated heart directly with induced current one minute. Marked fibrillary contractions result.

4:05. Respiratory movements still persist.

4:07. No pulse visible. Respiration ceased.

4:08. Heart still fibrillating. Applied adrenalin on surface.

4:14. Artificial respiration. Injected 10 c.c. of a mixture of 100 c.c. 0.9 per cent. sodium chloride and 1 c.c. of 1 to 1000 adrenalin chloride.

4:15. Heart still fibrillating.

4:16. 10 c.c. adrenalin injected.

4:17. 10 c.c. adrenalin injected.

4:18. Pressure unchanged in jugular vein. Injected 10 c.c. adrenalin.

4:19. 42 c.c. adrenalin injected. Ran in with very little pressure.

4:22. Pulse 130 a minute and feeble.

4:26. Stopped artificial respiration.

4:37. Injected 250 c.c. adrenalin solution.

4:39. Fibrillation of heart still feeble. No indication of rigor. Experiment discontinued.

Digitalein, which was used in rabbits only, gave results similar to those following the administration of adrenalin. The effect was more enduring than that of adrenalin, and the drug seemed, therefore, to be better adapted to the purpose.

Barium chloride was employed in a few experiments, but was abandoned as too dangerous and too uncertain. The regulation of

the dose is difficult and the secondary injurious action upon the walls of the blood vessels is a serious objection to its use.

Hydrogen peroxide, mixed with adrenalin and Locke's solution, has been used in successful resuscitations, but it is impossible to say in what degree the success was due to the peroxide.

Bandaging the limbs and abdomen, and particularly the latter, is of considerable value, owing to the intitial increase in the return of the blood to the heart in cases of hemorrhage, but it is of doubtful value where there has been no hemorrhage. When the blood volume is undiminished, it is relatively easy to produce over-distension and standstill of the right auricle by increasing the return of blood to it. Of course the diminution in the total vascular capacity tends to raise the blood pressure. The maximum increase in pressure produced by any ordinary bandaging is, of course, distinctly less than that produced by compression of the aorta.

The position of the body is of much importance, particularly where massage alone without intra-vascular injection is employed. We have thought that the advantage which experiment has clearly shown to be connected with the left lateral position might be associated with the easier return of the blood to the heart and possibly with a more favorable position of the ventricles for massage. The optimum position, as a rule, is attained by placing the animal on the left side and slightly elevating the posterior part of the body. When there has been no hemorrhage too great elevation of the posterior part of the body may easily cause over-distension of the right auricle and make resuscitation more difficult. In a number of experiments an increase of venous pressure corresponding to from 25 to 75 mm. of blood was sufficient to stop the right auricle. For example, in the experiment of March 1, 1905, quoted above, closing the outflow tube in the inferior vena cava stopped the auricular beats without affecting the rhythm of the superior vena cava.

Drugs introduced into the circulation can act upon the heart only when carried to it in the blood stream. It is obviously useless to try to start the heart which has completely stopped by subcutaneous injections of drugs. The addition of drugs which have a local action on the heart to fluids injected into the aorta may well have a beneficial effect. In case of the quiescent heart, drugs which

may beneficially affect the heart directly through its central nervous mechanism, *e. g.,* accelerator mechanism, or indirectly by raising peripheral vascular resistance can only exert their action if cardiac massage is combined with injection of fluid containing the drugs. Adrenalin chloride or any other drug which will constrict the arterioles, will be of service in increasing the arterial pressure and filling the coronary vessels.

In general, the mechanical methods for raising blood pressure are surer and more easily controlled than the methods involving the use of drugs. This agrees with Crile's observations on the treatment of surgical shock.

Electrical Stimulation of the Cardiac Nerves and of the Heart.—It has been shown by one of us (S.)[63] that stimulation of the augmentor nerves in the frog is capable of rousing a completely quiescent frog's heart from standstill.

Hering[64] has recently stated that rhythmical beats of the quiescent mammalian heart can be caused by stimulation of the nervi accelerantes. We have often seen beats produced in the hearts of cats and dogs by mechanical and electrical stimulation of the stellate ganglion or accelerator fibers. But we have not been able to cause complete resuscitation or restoration and maintenance of blood-pressure, which is a necessary condition for complete resuscitation by stimulation of the accelerantes alone.

We submit two condensed protocols of experiments showing the effect of mechanical stimulation of the accelerators. In the first one quoted, there can be little doubt that the heart had entirely ceased beating before the autopsy was made. Moreover, if such beats had persisted, they would have been noticed while the chest was open and the heart exposed. We regard this experiment as a demonstration that the heart may be caused to beat by stimulation of the accelerators after it has become completely quiescent.

Experiment of November 18, 1905.—Cat. Occlusion of cerebral arteries for twelve minutes. Cerebral circulation restored at 11:56 A. M. Spinal cord cut during anæmia. Artificial respiration maintained until 1:10 P. M. No spontaneous gasps occurred as long as cat was watched. On return to laboratory after lunch, there was every indication of death. No heart beat perceptible.

[63] Stewart, *Jour. of Physiol.,* 1893, xiii, 125. For other references see Stewart, *Amer. Jour. of Physiol.,* 1907, xx, 407.

[64] Hering, *Arch. f. d. gesam. Physiol.,* 1906, cxv, 354.

No respiration. Autopsy at 2:25 P. M.; while stripping fascia and pleura from cephalic vessels, the right auricle beat vigorously once. It beat again when the edge of it was pinched, with the forceps. Five beats were obtained by pulling at the fascia at some distance from the heart. Further attempts were not made. Ventricles did not contract.

While such a long time after heart stoppage did not elapse in the second experiment, we give the protocol, since it shows more specifically than the first the effects of mechanical stimulation of the accelerators, and the effects in this case extend to the ventricles as well as the auricles.

Experiment of April 19, 1906.—Large adult cat. Killed by etherization and bleeding at 3:45 P. M. Heart *in situ*. Artificial respiration employed. Pulmonary circulation left open.

4:00. Mixture of one-third defibrinated blood and two-thirds 0.9 per cent. sodium chloride solution injected into aorta. Auricles began to beat shortly after.

The heart beat for a time, then ceased entirely or went into fibrillary contractions. Luciani's groups appeared before final cessation.

4:19. Heart completely quiet. Pinching stellate ganglion of either right or left side causes a beat of the left auricle and ventricle. Right ventricle not observed. A separate beat follows every pinch.

The possibility of maintaining heart beat and blood pressure by electrical stimulation must therefore be admitted, and the work of Floresco,[65] while it must be received with some caution at the present time, may lead to important applications in the near future. The work of Mathews and Jackson[66] on the excitation of the heart in standstill produced by magnesium salts and of Floresco in standstill produced by asphyxia, showed the possibility of using this method in practical resuscitation and is worthy of investigation, but we have not made any experiments on it.

Certain variations from the classical effects of stimulation of the cardiac nerves have appeared in the course of the experiments. For example, in the experiment of February 14, 1905, stimulation of the accelerators caused no contraction of the heart in a small young dog whose blood had largely been replaced by Locke's solution, although the interval elapsing between the time of stoppage of the heart and the time of stimulation was not as long as the intervals after which successful results were obtained in other experiments. Later on in the same experiment, when the heart was

[65] Floresco, *loc. cit.*

[66] Mathews and Jackson, *Amer. Jour. of Physiol.*, 1907, xix, 5.

being perfused with defibrinated blood, the stimulation of the vagus caused marked strengthening of the heart contractions.

Experiment of February 16, 1905.—In a similar experiment on February 16, 1905, in which about 500 c.c. of blood had been removed from the carotid artery, stimulation of the central end of the cut right vago-sympathetic nerve, the left being intact, produced acceleration of the heart. Stimulation of the peripheral end of the same nerve produced still more marked acceleration. The latent period before acceleration began was remarkably long, and the acceleration increased as the stimulation was continued. The beats seemed to become stronger also. On injecting a mixture of two parts Locke's solution and one part of blood, the heart became stronger and the blood pressure rose. Stimulation of the peripheral end of the right vago-sympathetic nerve caused practically no effect; a subsequent stimulation caused a primary acceleration followed by some inhibition, and a slight fall in pressure.

The other (left) vagus trunk was then divided. Stimulation of its peripheral end caused inhibition of the heart and a fall of pressure. The first stimulation of the central end caused a rise of pressure. Subsequent stimulation of the central ends of both right and left vagi caused a fall in pressure. During the remainder of the experiment (about an hour) stimulation of the central ends of the vagi nearly always caused a rise in pressure. In four separate counts the rate of the heart (50 in 21½ seconds) was exactly the same before and during stimulation, although a good rise in blood pressure occurred after a somewhat long latent period in each instance.

In the experiment of March 1, 1905, in which artificial circulation was kept up, stimulation of the peripheral portion of the right vago-sympathetic caused no inhibition of the beats of the auricle and superior vena cava, but rather an acceleration.

A rise of blood pressure has frequently been noticed on stimulation of the central end of the dog's vago-sympathetic, but under normal conditions stimulation of the central end of the vagus in cats has given, without a single exception, a fall in blood pressure, with inhibition of the heart if the other vagus was intact.

The Fibrillary Contractions and the Means of Overcoming Them.—A troublesome feature of resuscitation of the heart is the fibrillary contractions which often appear as a sequel of massage or intra-arterial injections. Magrath and Kennedy[67] state that they have repeatedly seen the cat's heart recover from fibrillation after being in that condition for many minutes. D'Halluin[68] successfully added potassium chloride to the injected blood or other fluid to overcome the fibrillation of the heart. Herlitzka[69] in some

[67] Magrath and Kennedy, *loc. cit.*
[68] D'Halluin, *loc. cit.*
[69] Herlitzka, *loc. cit.*

cases used adrenalin chloride for this purpose, with considerable success. In experiments on the excised heart, where injection was made directly into the coronary artery, we had little difficulty with fibrillation. We have often encountered fibrillary contractions during massage of the heart *in situ,* but they have ceased if massage was continued and a sufficient blood pressure attained. For example, in the experiment of March 23, 1905, the protocol of which has been given above, fibrillation of the ventricles occurred after starting the heart by direct massage, but disappeared as the massage was continued from time to time, and the blood pressure increased. Sometimes it has been impossible to get the heart to beat regularly after the fibrillations have once begun. These fibrillary contractions and other irregularities of rhythm are, as a rule, more likely to occur when the salt solutions, *e. g.,* Locke's, are employed for injection or perfusion than when a proteid containing fluid, such as defibrinated blood, dilute serum, or the milk preparation above described is used. The most successful means of overcoming these contractions when they have appeared is, in our experience, an adequate circulation of the blood through the coronary vessels.

The following experiment shows that recovery from fibrillary contractions may occur suddenly.

Experiment of May 16, 1905.—Adult male cat. Ether. Tube in larynx in which there was an occlusion of twenty-one minutes; the heart stopped about sixteen minutes after the release of the head arteries. Massage of the chest was tried, to no purpose. About fifteen minutes after the heart stopped, the thorax was opened, the aorta clamped and the heart massaged directly. Heart entirely motionless at the time the chest was opened. In five minutes the auricles were beating well, and the ventricles fibrillating. The auricles began to beat very soon after massage was begun, but the ventricles not for some time. Suddenly, seven minutes after the chest was opened, the ventricles began to beat well. No further massage was needed throughout the experiment, which was continued for five hours longer; when it was discontinued, the heart was still beating excellently.

Resuscitation of the Regulative Mechanisms of the Heart.—The question is an interesting one whether the cardiac regulative mechanisms are rsuscitated at the same time as the automatic beat. The answer is, that in general the central innervation of the heart, both accelerator and inhibitory, is in abeyance for a longer or shorter period after the spontaneous beat of the heart has been restored,

the length of this period depending on the time of occlusion. The same is true of the local regulative mechanism which we have treated of in a previous paper.[70] For example, while in the normal heart the rate is diminished by increase of coronary pressure and increased by diminution of pressure in the heart, during resuscitation there is a period when increase of pressure is accompanied by increase in the rate and vice versa, just as happens in the excised heart. This fact suggests that the local mechanism which in the normal heart even in the absence of extrinsic innervation causes the response of diminished rate to increased pressure and increased rate to diminished pressure has not yet been restored. After long periods of asphyxia no restoration may ever take place. As regards the mechanism, whatever it may be, which normally coördinates the contraction of the two ventricles and renders it synchronous, it seems to be resuscitated as soon at any rate as the power of the ventricles to beat, since when the ventricular beat appears it is found to start synchronously on the two sides. This is in favor of the view that no specific mechanism is concerned in this coördination.

Arhythmia of auricles and ventricles and Luciani's groups are fairly common phenomena in the resuscitation of the heart *in situ* or in perfusion of the excised heart. Arhythmia of the auricle and ventricles was noticed in the experiment of March 1, 1905, already quoted. In the same experiment, a more rare phenomenon was observed, namely, arhythmia of the superior vena cava and the auricles.

In many of the experiments the heart, during the resuscitation following cerebral anæmia, is generally beating as fast as hearts whose vagi have been cut, although stimulation of the peripheral end of the vagus stops or slows them. This, we believe, indicates that the vagus center has not recovered its tone, although its endings are intact. The significance of this will be considered further in the section on the cardio-inhibitory center. During the inactivity of the vagus center, however, asphyxial slowing of the heart occurs as usual. Since we have shown that asphyxial slowing of the heart may result after section of both vagi and division of the cervical spinal cord, we conclude that the action may be local, and not necessarily central.

[70] Guthrie and Pike, *loc. cit.*

We[71] have called attention in another paper to the peculiar double beat appearing in the tracing of the excised heart when the pressure of injection is low. A similar double beat frequently occurs at a certain stage in the occlusion period, as is shown in the following experiment.

Experiment of May 29, 1905.—Adult male cat. Ether. Tube in larynx. Pulse (under ether before experiment) 207 a minute. Respiration about 60 a minute.

2:50 P. M. Occluded head arteries in usual way.
2:50:15. Respiration rapid and shallow.
2:50:25. Corneal reflex gone.
2:50:40. Natural respiration stopped. Started artificial respiration.
2:51:45. Pupils same as before occlusion, not at all dilated.
2:52:30. Pupils dilating.
2:53. A gasp (secondary series).
2:53:20. Pulse had double beat usually seen at this stage.
2:53:30. Pulse 216 in the minute.
2:54:05. Double beat of pulse gone.
2:54:30. Gasps still going on.
2:57:30. Gasps cease. Pupils at maximum dilation.

From a study of the above excerpt from the protocol of the experiment, it will be seen that the double beat appears only during the time in which the cardiac and other bulbar centers remain active, and that it ceases at about the time that the inhibitory center fails. Since the heart goes on with machine-like regularity after the total failure of the bulbar centers, there seems little doubt that the double beat is caused, in the case of the heart *in situ* by the extrinsic cardiac nervous mechanism, and since, furthermore, it appears during the time of the activity of the inhibitory mechanism, it is possible that this double beat is a phenomenon of inhibition.

Resuscitation of the Heart after Death from Other Causes.—From a considerable number of experiments we conclude that chloroform has the most deleterious action, the A. C. E. mixture coming next in order, and then ether. All our evidence tends to corroborate the current statement that chloroform acts very injuriously on the heart tissue. Morphine, when used subcutaneously in addition to any of the other anæsthetics, tended, as a rule, to make resuscitation less successful.

Hemorrhage complicated the result here as well as in asphyxia.

[71] *Amer. Jour. of Physiol.*, 1907, xviii, 24.

The hemorrhage was always carried out under general anæsthesia.

One cause of the greater difficulty of resuscitation attending death from hemorrhage is the absence of a sufficient volume of nutritive fluid. So we must first supply a certain volume of fluid of a suitable nature, and afterwards get it in motion. A fluid as good as serum or blood can only be obtained by transfusion. As we have not empolyed this method, adhering to blood dilutions and artificial liquids, it can not be stated definitely whether hemorrhage in itself, by sooner exhausting the supply of nutriment of the tissues than would be the case where the circulation is simply stopped, or by robbing the lymph unduly of water, renders resuscitation more difficult, even under the influence of a copious supply of transfused blood. Judging from our work upon the excised mammalian heart, the milk preparation which we then employed would be more suitable for intra-vascular injection after hemorrhage than the salt solutions.

Resuscitation after Electrocution.—Our first experiments on resuscitation after electrocution were made in 1901. They were not satisfactory because of the low voltage (110 volts, direct) of the currents available for the purpose. Sponges were connected with the ends of the wires and used as electrodes. One was placed on each side of the thorax of an anæsthetized dog. The circulation was but little affected even after some minutes.

Direct stimulation of the heart with induced currents caused delirium cordis. The restoration of the circulation afterward was not very successful, owing to the difficulty of overcoming the delirium. Cold, asphyxia and the methods generally recommended for the purpose were quite inefficient in our hands. Resuscitation appeared more difficult than after asphyxia, anæsthetics or hemorrhage. Later on, when Dr. Crile began a series of experiments on the same subject with a much more powerful instalment, we allowed the matter to drop.

SUMMARY.

Our results may be briefly summarized:

1. Blood, when defibrinated, soon loses its power to maintain the activity of the higher nervous centers, and its nutritive properties for all tissues quickly diminish.

2. Artificial fluids, as a substitute for blood, are not satisfactory.

3. The proper oxygenation of the blood is an indispensable adjunct in the resuscitation of an animal.

4. The heart usually continues to beat for some minutes after it ceases to affect a mercury manometer, and resuscitation of it within this period by extra-thoracic massage and artificial respiration is sometimes successful.

5. Resuscitation of the heart by direct massage is the most certain method at our command.

6. A proper blood-pressure is an indispensable condition for the continued normal activity of the heart.

7. Anæsthetics, hemorrhage and induced currents applied to the heart render resuscitation more difficult than asphyxia alone.