STUDIES IN RESUSCITATION: IV. THE RETURN OF FUNCTION IN THE CENTRAL NERVOUS SYSTEM AFTER TEMPORARY CEREBRAL ANÆMIA.[1]

BY F. H. PIKE, C. C. GUTHRIE AND G. N. STEWART.

(From the Hull Physiological Laboratory, University of Chicago.)

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I. INTRODUCTION.

The experiments on the resuscitation of the central nervous system were begun more than three years ago. The primary object was to test the possible length of time elapsing after death, after which the return of all the nervous processes could be hoped for, since we had good reason for believing that the central nervous system would prove a weak link in the vital chain, but the further possibility of obtaining new data on some of the nervous processes soon became apparent.

We have described in other papers[2] the main phenomena of resuscitation of the central nervous system after cerebral anæmia. Here we shall briefly summarize the results of the resuscitation of the central nervous system as related particularly to the resuscitation of the entire animal body and incorporate at greater length some new observations on the more strictly physiological phase. Our work has dealt almost entirely with resuscitation after total anæmia except that, rarely, from some slip in technique or, more commonly, for some anatomical reason, the brain and upper cer-

[1] Received for publication April 16, 1908. The previous papers in this series have appeared in the *Journal of Experimental Medicine*, 1908, x, 371; the *American Journal of Physiology*, 1908, xxi, 359, and xxii, 51.

[2] Stewart, Guthrie, Burns and Pike, *Jour. of Exper. Med.*, 1906, viii, 289; Guthrie, Pike and Stewart, *Amer. Jour. of Physiol.*, 1906, xvii, 344; Stewart and Pike, *ibid.*, 1907, xix, 328; xx, 61; Stewart, *ibid.*, 1907, xx, 407.

vical cord still obtained a small amount of blood. Hill[3] states that "the merest dribble of blood" suffices to maintain a certain degree of activity of the central nervous system for long periods. To this we can fully subscribe. It is possible, also, that the mere presence of blood in the vessels, although completely stagnant, may help to prolong the period of resistance of the tissues to definitive death, so that it may not be indifferent whether the interference with the nutrition of the central nervous system is produced by occlusion of the whole arterial path to the central nervous system, as in most of our experiments, or by simple cessation of the circulation due to stoppage of the heart or, finally, by such a process as strangulation, which occludes simultaneously the arteries and veins. It is obvious that the greatest and most severe anæmia will be caused by the first method, a less complete and more gradual anæmia by the second, while the third will leave the normal amount of blood in the organ practically unchanged. The results of Ségalas d'Etchepare,[4] who found that the struggles of the animal persisted longer after ligation of the abdominal aorta when the inferior vena cava was also occluded than when the aorta alone was tied, would seem to indicate that stagnant blood is better than no blood at all in contact with the tissues. It is possible that such differences account, to a certain extent, for the discrepancies in the literature as to the length of time the circulation in the central nervous system can be stopped without rendering resuscitation impossible.

D'Halluin[5] states that the secondary alterations of the central nervous system following anæmia are not immediately fatal nor without remedy. He does not believe that Battelli's[6] limit of twenty minutes after cessation of the respiration is the absolute one for the resuscitation of the central nervous system, and is inclined to believe that there is experimental as well as clinical evidence that the central nervous system is capable of resuscitation after periods of perhaps relative but very prolonged anæmia. Green[7] states that in one of his cases, a boy nine years old, the

[3] Hill, *Philos. Transactions of the Royal Soc.*, 1900, cxciii, 121.

[4] Ségalas d'Etchepare, *Jour. de physiol. expér. et path.* de Magendie, 1824, iv, 287; cited by Batelli, *Jour. de physiol. et path. générale,* 1900, ii, 443.

[5] D'Halluin, *Presse méd.,* 1904, xii, 345.

[6] Battelli, *Jour. de physiol. et path. générale,* 1900, ii, 443.

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

heart was not started by massage until twenty-five minutes after it first stopped, and did not beat strongly until thirty-five minutes after it first stopped. Severe spasms, rapid respiration (40) and pulse (168 in the minute), perspiration and high temperature followed, with death in twenty hours. This case might seem to lend some slight support to D'Halluin's conclusions. We have already pointed out in another place that the time of heart stoppage is impossible to determine except by actual inspection. For this reason we must exclude as evidence many of the clinical cases reported and cited in support of a longer limit, after which resuscitation is possible. We are not inclined, therefore, to give much weight to D'Halluin's contention.

Our experience, on the contrary, is that Mayer's[8] limit of ten to fifteen minutes of total cerebral anæmia, beyond which resuscitation is not possible, is approximately correct. This limit may be extended a little, but not a great deal, where the circulation has stopped completely without causing the extreme anæmia produced by our technique.

The exact moment at which the heart stops beating can be determined by inspection; and the last respiratory movement may easily be observed and recorded. Similarly, in the restoration of these systems to activity, the direct observation of the first movement is not a matter of great difficulty. The determination of the state of the cortical centers is somewhat different. There are, except in the case of the motor cortex in general, no unequivocal and objective signs of the loss or return of function.

In considering the resuscitation of the central nervous system we may most conveniently deal first with the return of the various functions and reflexes separately, considering them as criteria of the physiological condition of their respective centers. We will take up, therefore, the resusciation of the bulbar centers and then the return of the functions of the higher centers.

II. THE RESUSCITATION OF THE BULBAR NERVOUS MECHANISMS.

The Resuscitation of the Extrinsic Cardiac Nervous Mechanism.—The heart continues to beat in cerebral anæmia, apparently little

[8] Mayer, *Med. Cent.*, 1878, xvi, 579.

affected, long after the failure of all the cerebral centers, and even when the vagi, the cervical sympathetic, and the spinal cord are divided. Furthermore, a dog's heart will continue to beat for several hours after the removal of the head. It seems certain therefore, that the mammalian heart will beat without receiving any impulses from the brain. But will the heart beat continue indefinitely in the absence of cerebral impulses? So far, the only experimental answer to this question is that of Friedenthal[9] who severed all the cardiac nerves of rabbits, including the sympathetic, and all of the vagus except the Hering-Breüer fibers to the lungs. The animals lived for several months without suffering any great inconvenience during ordinary activities. We have observed some instances in the course of our experiment which would seem to be incompatible with Friedenthal's conclusions, but the question cannot be discussed here.

Asphyxial slowing of the heart may occur at any time during cerebral anæmia; and even when both vagi and the spinal cord are divided. The heart rhythm after restoration of the cerebral circulation, shown in detail in the tables in our previous papers, may indicate disturbances of the vagus center for several days afterward. Certain other influences, such as hyperthermia, may also enter in to affect the rate, and obscure the vagus effect. Quite apart from these, however, the vagus effect usually returns along with the function of the other bulbar centers, after which it may apparently fail for a time, perhaps several days, and then again finally recover its functional control of the heart.

The question of the nature of the origin of the vagus tone —whether reflex or automatic—has been discussed in a separate paper.[10] In the present paper we will offer some new evidence bearing on this question. We may, for example, investigate the relation between the first appearance of the vagus tone in the resuscitation period, and the first appearance of the vaso-motor tone. If the vagus tone is of automatic or central origin, we would expect a gradual decrease in the pulse rate as the blood pressure rises. As we have pointed out in the first paper of the

[9] Friedenthal, *Arch. f. Physiol.*, 1902, 135.
[10] Stewart and Pike, *Amer. Jour. of Physiol.*, 1907, xix, 328.

present series, the rate of the heart in the resuscitation period is that of a heart whose vagi have been divided, although the vagus endings in the heart are perfectly active. The heart maintains a practically constant, or even an increasingly high, rate as the blood pressure gradually rises. This evidence, as far as it goes, does not show the existence of an automatic element in the vagus tone. If now we investigate the time relations of the first appearance of vagus tone and the opening up of the reflex pathways for vagus inhibition, we find a very close correspondence in the time of their appearance—that is, there is little or no vagus tone discoverable in the resuscitation period until the integrity of the reflex arc is restored. There is, then, not only no evidence in favor of an automatic or central origin of the vagus tone, but also, as we have shown elsewhere, direct evidence in favor of its reflex origin.

Couty[11] states that the cord constitutes an independent cardiac accelerator mechanism as well as a vasomotor center, modified by anæmia, asphyxia and other influences. Couty used lycopodium spores, injected into the cerebral arteries, to produce anæmia of the brain. In all our experiments in which we were certain that the bulbar centers had ceased to function, we were unable to get the normal increase in heart rate by suddenly lowering the blood pressure. The heart beats on with machine-like regularity during the occlusion period. Barring the possibility of spinal shock in our experiments, we do not consider it probable that accelerator impulses normally arise from the cord below the fourth cervical segment—the lower level of total anæmia in most of our experiments, but we do not deny the possibility that a phylogenetically more primitive mechanism located in the cord, might, under proper conditions, again become active and discharge accelerator impulses to the heart.

One other line of evidence not previously considered remains to be examined, and that is the correspondence in the time of resuscitation of such a mechanism as that for swallowing, which is so evidently reflex, and the return of the vagus tone. But since, as is self evident, the same questions arise in connection with vasomotor tone and respiration, and the same standard of comparison may be

[11] Couty, *Arch. de physiol. norm. et path.*, 1876, Ser. 2, iii, 665.

used in determining their origin, we will first present the facts with regard to these mechanisms and then attempt their interpretation.

The Resuscitation of the Respiratory Nervous Mechanism.—It is obvious that, for the continued life of an animal the resuscitation of the respiratory mechanism is a matter of necessity. The heart may be beating vigorously and the tissues be well nourished so long as oxygen is provided by artificial means, but unless spontaneous respiration occurs, sooner or later death is inevitable. The choice of a method for starting the heart will therefore depend not only upon its efficiency in restoring cardiac function, but also upon the facility with which we may direct a stream of oxygenated blood through the medulla oblongata.

We have considered, in other papers, the resuscitation of the respiratory center after cerebral anæmia in much detail, and we have devoted particular attention to the question of the automaticity of the respiratory center.[12] The resuscitation of the respiratory center after asphyxia and other forms of death is very much the same as after cerebral anæmia provided the period of asphyxia has been reasonably long. There is, in general, the same strong first gasp, and the slow initial rhythm which gradually increases to the normal rate. The time required for recovery from transient respiratory failure due to anæsthesia is, of course, much shorter than that required for recovery from prolonged bulbar anæmia.

The regularity and constancy of the initial respiratory rhythm in resuscitation, three to five a minute, and the similarity of this rhythm to that sometimes observed after section of both vagi, and particularly after section of the higher pathways to the brain, is one argument we have advanced in favor of the automaticity of this center. The further fact that this slow, regular rhythm may persist for a time, the length of which depends partly upon the gravity of the injury to the cells, unaffected by stimulation of the afferent nerves is also an indication that the center is functioning in the absence of afferent impulses—*i. e.*, the center is automatic.

In a small dog (Experiment 1, March 13, 1905)[13] it was noted during the whole time of compression (three minutes and five seconds) of the arch of

[12] Stewart and Pike, *Amer. Jour. of Physiol.*, 1907, xix, 328.

[13] The experiments are numbered consecutively for convenience in reference. The chronological order is indicated by the dates given.

the aorta and of the innominate artery, that inspiratory acceleration of the heart occurred with each natural respiration, but not with artificial respiration. The impulses discharged from the respiratory to the cardiac center were not, therefore, reflex from the pulmonary fibers of the vagus. The quickening of the heart toward the end of the inspiration has been observed, in our later experiments, at a time when the afferent impulses did not affect the respiration.

Certain other structures participate in the respiratory activity by associated movements, notably among these being the eyelids.

For example, in Experiment 2, after an occlusion of sixteen minutes in a cat, the respiration was going on 34 minutes after the release at the rate of twelve in a minute. The movements were strong and extensive, the whole head participating in them. There were also strong fibrillary contractions of the tongue, and violent twitching movements of the vibrissæ. The pupils were well contracted, but there was no corneal, light or lid reflex. The animal winked its eyes slightly but distinctly, the upper eyelid descending with each respiratory movement. Again, in Experiment 3 (June 7, 1905), 28 minutes after an occlusion of 31 minutes, the pupils were well contracted, and the light reflex had returned, but not the corneal. The respirations at this time were rapid and in groups of four or five, getting progressively stronger up to a maximum. Strong nostril movements accompanied the respiratory movements. The eyelids moved with the strong respiratory gasps, the aperture of the eye widening, but not with the weak gasps.

The synchronism of the natural with the artificial respiration is a peculiar phenomenon seen in some of the experiments. An instance of this occurs in

Experiment 4 (March 29, 1905). Half grown cat. Ether. Tracheotomy. Artificial respiration. Opened chest.

1:40:15 P. M. Clamped aorta just above intercostal branches.

1:41. Clamped innominate and left subclavian arteries.

2:01. Released innominate and left subclavian arteries.

2:06. A gasp.

2:06:20. Another gasp. Gasping respiration goes on regularly, five in the minute.

2:11. No movements on striking forelimb.

2:12. Respiration strong and extensive, eight a minute.

2:14. Respiration 12 a minute, including some small respiratory movements one of which sometimes precedes a deep one. No movement elicited by striking the forelimb.

2:17. No light, lid, corneal, or ear reflexes. The respiration often commences with a rather prolonged, slight opening of the mouth, which ends in a wide gasp.

2:21. Pupil contracted down to a slit. No light reflex.

2:23. No eye or ear reflexes. No movements on pinching ear or on striking forelimbs. Temperature 33° C. in the thorax.

2:28. Swallowing movement.

2:30. The natural respiration is now synchronous with the artificial, ten in 18 seconds, extending to nose, mouth and chest.

2:33. On striking forepaw, get movement of same limb and very slight movement of the opposite shoulder.

2:34. No eye or ear reflexes. Pupils still slits. The natural respiration continues synchronous with the artificial.

2:37. On touching cornea, the eye seems to water, although the eyelids do not move. Marked movement of forelimb on striking it; also movement of opposite forelimb.

2:43. Fair corneal reflex. No light reflex. Strong movement of forelimb when struck and weaker but distinct movement of opposite forelimb.

2:45. Strong light causes marked closing of eyelids but no change in the pupil. Repeated many times.

2:50. Corneal reflex quite marked; also the foreleg reflex, which crosses from either side. Stopped artificial respiration. Cat breathes slowly by itself. Started artificial respiration again.

2:55. The forelimbs are extended and getting stiff. Light reflex is present in pupil.

3:00. Winks eye when ear is flicked. No ear reflex.

3:10. On pinching larynx, get a swallowing movement every time. (Stimulation of superior laryngeal?)

3:15. Stimulated left vago-sympathetic. Causes stoppage of heart, maximum dilation of pupil, bulging of eye and retraction of nictitating membrane.

At times the synchronism assumes a different form.

Thus, in Experiment 5 (March 21, 1905), beginning about twenty minutes after the head arteries were occluded, the cat inspired synchronously with the artificial inflation of the lungs, but only half as often. Twenty-two minutes from the beginning of the imperfect occlusion, natural expiration occurred synchronously with the inflation of the lungs, and exactly half as often. The occlusion lasted, in all, 30 minutes. Fourteen minutes after the release of the head arteries, the artificial respiration was interrupted, and the cat, which had been, for several minutes, breathing synchronously with the artificial respiration, went on breathing for 25 seconds with exactly the same rhythm.

Such instances are too common to be mere coincidences.

Apnœa during the resuscitation period is not uncommon. Instances of this have been given in previous papers. In one experiment, lowering the systemic blood pressure apparently again started respiration. Other cases in which hemorrhage or trephining the skull caused the apnœa to cease, *e. g.*, in Experiment 16, the protocol of which is given later on, have been encountered.

In Experiment 6 (May 13, 1905), three hours after release following an occlusion of one hour, stopping the artificial respiration caused respiratory movements to begin after a considerable interval. These movements involved, at first, the diaphragm alone and later on, the ribs also. Apnœa had lasted two hours.

Well-marked periodic respiration of the Cheyne-Stokes type sometimes occurs well on in the resuscitation period.

In Experiment 7 (May 2, 1905) the first gasp occurred fifteen minutes after a release from an occlusion of 30 minutes. The first gasps occurred at the rate of four in 64 seconds. About four hours after release, the respiration was 140 per minute, with strong associated movements of the nostrils. Pressing the fingers over the chest on each side of the sternum caused marked slowing of the respiration, persisting as long as the pressure was maintained. Twenty-five minutes later, repeating the pressure over the chest caused the same slowing of respiration. The respiratory rate was, at this time (7:38 P. M.), 100 a minute but there were marked variations in the rate at successive intervals of a few seconds. At 8:13, the hind end of the animal was elevated to allow fluid and mucus to run out of the mouth. The respiration decreased to 86 a minute for two or three minutes, but the rate soon rose again. At 8:18, the hind end was lowered again, and the respiratory rate fell to 84 a minute. Then, with the board in exactly the same position, the respiration rose to 100 a minute at 8:32, then to 144 at 8:38, to fall again to 106 at 8:46, and to 84 under the influence of a small amount of ether at 9:00 P. M. An hour later, the respiratory rate was 59 in the minute.

Movements closely approximating spinal respiration have also been observed. One example of this has been given in a previous paper,[14] in which we described also the reflexes simulating respiratory movements so readily obtained through the spinal cord in the resuscitation period following prolonged occlusions. One other case is of interest in this connection.

In Experiment 8 (May 22, 1905), two hours and forty-seven minutes after release following an occlusion of 60 minutes, abdominal movements began. Twenty-four minutes afterwards, on stopping artificial respiration, these movements spread upward to the thorax, producing fair ventilation of the lungs for three minutes, after which artificial respiration had to be started again as signs of asphyxia (stiffening of the forelimbs in extensor spasm) came on. The same series of events was repeated 46 minutes later. True bulbar respiration never returned.

This phenomenon has been observed so frequently that we may say, almost as a general rule, that in those cats which do not recover the power of normal permanent breathing of the bulbar type, imperfect respiratory movements seem to start from the lower part of the cord involving the hind legs and abdomen and then, if sufficiently strong, extending up to the thorax.

The Resuscitation of the Bulbar Vasomotor Mechanism.—We

[14] Stewart and Pike, *Amer. Jour. of Physiol.*, 1907, xix, 339.

have given in another place[15] the physical requirements, in the matter of a suitable blood pressure, for the continued activity of the heart. Still more striking examples are given by Goltz.[16] In dogs whose spinal cord had been transected in the lower dorsal region and allowed to recover, destruction of the cord below the level of the transection was followed by death in thirty hours or less. According to Goltz the cause of death was the low blood pressure.

It is clear, from a consideration of these facts, that a certain blood pressure is necessary for the continued action of the heart and respiratory mechanism. So long as the peripheral vessels remain widely dilated, and the blood passes through with relatively little resistance, this condition will not be fulfilled. The arterioles must be constricted to their normal diameter, the splanchnic vessels must give up their enormous volume of stagnant blood, and the natural resistance to the blood flow be reëstablished. All this is a part of the work of the vasomotor mechanism. Before an animal can be considered as resuscitated, we must, therefore, restore the system or center which maintains the necessary blood pressure. In selecting a method for starting the heart, we must keep in mind that it is necessary to maintain, or very soon to establish, a circulation through the respiratory and vasomotor centers, particularly through the latter. If a blood pressure sufficient for the activity of the heart can be maintained, the oxygenation of the blood can easily be accomplished. The maintenance of a sufficient blood pressure by any means which is not in itself injurious, or which does not curtail the flow of blood through the vasomotor and respiratory centers is, however, far from easy of accomplishment. Aside from the resuscitation of the cortical centers, to be discussed in a subsequent section, we may regard the restoration of the vasomotor center as the completion of the final link in the vital chain.

The Relative Resistances of the Vasomotor and Respiratory Centers to Cerebral Anæmia.—The exact moment at which the vasomotor center ceases to function is not so easy to determine as the time at which the respiratory center fails, as there is no such

[15] Pike, Guthrie and Stewart, *Jour. of Exper. Med.*, 1908, x, 371.
[16] Goltz, *Archiv für die gesammte Physiologie*, 1873, viii, 460.

sudden cessation of a very noticeable phenomenon connected with the former as with the latter mechanism. Instead of a last great movement, the vasomotor center fails gradually, and the time of cessation of function is further masked by the fact that there are accessory vasomotor centers in some animals which assume a part of the function of the medullary center on the failure of the latter. It is our opinion that the vasomotor center is more resistant to anæmia than the respiratory center, and attains a certain degree of functional activity after the restoration of the cerebral circulation before the respiratory center gives any sign of its activity. In this condition, we must remember that a part of the vasomotor mechanism is not subjected to anæmia, while no accessory respiratory centers concerned in the first movements in the resuscitation period exist outside the medulla oblongata. We are therefore restoring only a part of a system in the first case and a whole system in the second. In order to make conditions strictly comparable, we must destroy the function of all vasomotor centers as well. This is accomplished in asphyxia or any other form of general death. Exact observations, aside from Hayem's[17] work on death from hemorrhage, are not at hand in sufficient numbers to decide unequivocally which center persists longer in general death, but we believe that the vasomotor center is the more resistant, and that it is also somewhat easier to restore to a certain degree of functional activity than the former center. In cerebral anæmia, with all the systemic vessels, aside from those of the head open, Traube-Hering curves have sometimes appeared in the blood pressure tracing after total cessation of respiratory movements. In these experiments, it must be assumed that the vasomotor center is the more tenacious of life.

We have previously discussed the condition of the vasomotor centers in the spinal cord, and will quote only one new experiment here.

The pads on the hind foot of a cat, when placed in contact with ice, became very red at a time in the resuscitation period when no eye reflexes had returned and when the bulbar vasomotor center had, in all probability, not recovered its tone. The reaction was brought about, therefore, either through the vasomotors of the cord, or through a local mechanism.

[17] Hayem, *Arch. de physiol. norm. et path.*, 1888, Ser. 5, i, 103.

Although the spinal cord centers, or what we have supposed to be spinal vasomotor centers, maintain a fair blood pressure in the absence of the cerebral centers, unequivocal reflexes are not easy to obtain through the former, at least in the occlusion period and early in resuscitation. There seems to be a marked automatic element in their activity, but further work on this point is necessary. It is possible that this absence of spinal vasomotor reflexes, as we will point out later, may be due to spinal shock.

The tonicity of the bulbar vasomotor mechanism begins to return, in the resuscitation period, as a rule before the respiratory center begins to discharge, and, as is the case with the respiratory center, there is often a period during which the blood pressure may be rising, but when reflex changes in pressure do not occur through stimulation of the vagus or brachial nerves. Similarly, a time may often be found in the occlusion period when the blood pressure is still high, and the bulbar vasomotor mechanism undoubtedly functional, when stimulation of the afferent nerves produces no effect on the blood-pressure curve. We have attributed the persistence of pressure after the cessation of the reflex effects, and this early rise in pressure before the opening up of the reflex pathways to the automaticity of the nervous mechanism involved.

TABLE I.

Showing the length of the occlusion period and the time of return of deglutition, as compared with the return of respiration.

Date.	Length of Occlusion.	Time after Release of First Gasp.	Time after Release of First Swallowing Movement.
March 3, '05	6 minutes	40 seconds	3½ minutes
March 18, '05	12 min. 45 sec. Heart stopped 15 to 20 min. Started by massage.	Less than 38 min.	52 minutes
March 29, '05	10 minutes	5 min. 40 sec.	14½ minutes. Several movements.
March 29, '05	20 minutes	5 minutes	27 minutes
June 7, '05	31 minutes	9 minutes	6 hours

Considered either from the view point of resistance during the occlusion period, or the return of function during the resuscitation period, the respiratory and vasomotor mechanisms show a greater vitality than either the extrinsic cardiac or the swallowing mechanisms.

The Resuscitation of the Swallowing Mechanism.—The resuscitation of this mechanism is of peculiar interest from the fact that swallowing is so clearly a reflex act. The time in the resuscitation period at which the first swallowing movement was observed is given in Table I. In all experiments the respiration returned a considerable time before swallowing was observed. In all experiments, too, the blood pressure had risen to a considerable height. Swallowing has, however, been observed before the return of the eye, ear or fore-limb reflexes. Experiment 4 may be cited as a case in point. After long occlusions, swallowing has been observed to return along with the rolling movements of the eyes and the secretion of tears a considerable time after the restoration of the cerebral circulation, *e. g.*, in one experiment, six hours after an occlusion of thirty-one minutes.

When the order of disappearance of the reflexes and functions of the bulbar centers is studied, it will be noted that swallowing may persist longer than the corneal or light reflexes, but ceases before the end of the secondary series of respiratory gasps or the failure of the vasomotor center. The time relations of the cessation of some of these functions are shown in the following protocol.

Experiment 9.—(April 19, 1905.) Cat. Ether. Tube in larynx.

3:12 P. M. Occluded head arteries.

3:12:15. Corneal reflex gone. Respiration stopped, pupils dilated, legs straightened out. Started artificial respiration.

3:12:25. Swallowed.

3:12:48. A slight respiratory movement.

3:13:05. Another slight respiratory movement.

3:13:15. Pupil about one half maximal dilation. Several strong swallowing movements.

3:13:40. Pupils now much wider, nearly maximum. A strong gasp occurred.

3:14:05. Several strong gasps in quick succession, and kicking movements of hind limbs.

3:15. Struggling of whole body, except head. Tail lashing violently for a long time.

3:15:30. Strong struggling movements. Strong lashing of tail, and scratching movements of hind limbs.

3:16:05. All movements stopped. There have been no respiratory movements for a minute.

3:18. Pulse 258 in the minute.

3:19:20. Hind limbs now quite limp. *No response on pulling or striking.*

3:22. Put thermometer into rectum. Hips twitching when thermometer was passed. Rhythmical contraction of rectal and vaginal sphincters going on. Temperature 36½° C.

3:25:30. Moving thermometer in rectum causes contraction of vaginal and rectal sphincters and whole perineum.

3:30:15. Released head arteries.

3:42. Good kicking movements of hind legs on putting thermometer into rectum. Rhythmical movements of rectal sphincter, about twelve a minute.

In this experiment, the persistence of the swallowing mechanism is intermediate between that of the eye reflexes and of the bulbar respiratory and cardiac mechanisms. The same time relations appear in many other experiments, and we have never observed the persistence of swallowing after the respiration had permanently ceased, or the blood pressure fallen very low in the occlusion period.

The activity of the swallowing center, as we have shown in another place, may be conserved for a time when other fluids are substituted for blood.

The effect of the fresh defibrinated blood, artificially circulated through the head of a dog, in maintaining the irritability of the œsophagus and the integrity of the nerve endings in the tongue, and upon the submaxillary glands and the sympathetic endings in the pupil as well, is shown in the following experiment.

Experiment 10.—(February 28, 1905.) Medium sized dog. Ether.

2:40 P. M. Drew off 830 c.c. blood. Began artificial respiration.

3:15. Tied aorta and put cannula in the central end. Heart soon stopped.

3:26. After elevating hind end and bandaging abdomen, tied inferior vena cava and put cannula in heart end. Tied subclavian arteries and veins.

3:29. Tied a ligature around heart in auriculo-ventricular groove, leaving out inferior and superior cavæ. No eye reflexes.

3:30. Started artificial circulation with a double bottle arrangement. The blood would not run out of the cannula in inferior cava, although the auricle and superior cava and inferior cava down to the cannula were full. Removed clot. Blood now runs off.

3:40. Circulation was really started.

3:48. Stimulated left vago-sympathetic, in continuity, without tying. Good bulging of the eye and dilation of pupil. Secretion, or possibly liquid gastric contents, started to flow from the nose. There were a few drops before, but it is now much increased. The pupils have narrowed considerably since the artificial circulation started.

3:50. Stimulated right vago-sympathetic, in continuity, without tying. Marked bulging of the eye, opening of palpebral fissure, and dilation of pupil.

3:59. Still considerable liquid dropping from nose. Good bulging of eyes on stimulation of the vago-sympathetics.

4:02. Opening of left eye and dilation of the pupil on stimulation of vago-sympathetic. Immediately after stimulation much liquid runs out of mouth and nose, evidently from the œsophagus, and contains small granules of food.

Either the œsophagus contained liquid, which stimulation of the vagus caused it to expel, by causing contraction, or vomiting was caused from the stomach by vagus stimulation. The mucous membrane of the mouth and tongue is moist and well flushed with blood. Vaso-dilation seems to be present.

4:23. Marked dilation of pupil and bulging of right eye on stimulation of right vago-sympathetic. Exposed left chorda tympani and Wharton's duct. The duct is empty. Stimulation of chorda does not cause filling of duct.

4:35. Stimulated each vago-sympathetic. Marked opening of eyes but now little or no dilation of pupil. Stimulated central end of left lingual nerve. No reflex movements.

4:43. Stimulation of left vago-sympathetic causes marked bulging of eye, some retraction of nictitating membrane and slight dilation of pupil.

4:46. Stimulation of left hypoglossal nerve causes strong contraction of tongue. Motor endings intact.

4:53. Trephined and stimulated motor area on right side. No effects of any kind. No eye movements nor change in pupil on left side. No movements of neck nor left forelimb. The jaws are now showing some rigor (decerebrate rigidity?). Stimulated left vago-sympathetic. Fair dilation of pupil.

4:55. Again stimulated right motor cortex. No effect even with strong stimulation. Cut out gray matter and stimulated corona radiata. No effect. Stimulated axillary nerves on left side. Good contraction of muscles. Direct stimulation also caused good contraction. Stimulated œsophagus. Good contraction. The œsophagus seems to retain its excitability better than anything else in the neck. Stimulated left sciatic nerve. No effect either direct or reflex. Stimulated hind leg muscles directly; no effect.

On post mortem, found air bubbles in vessels at base of brain, *e. g.*, basilar, and also on cortex.

All through this experiment from the time the artificial circulation was properly started, the flow of blood was good and the carotids showed a good pressure. The blood was in an air-pressure bottle under about 100 mm. Hg.

It will be noted that the peripheral nerves and muscles, and particularly the œsophagus, retained their irritability for a considerable time after the motor cortex became inexcitable. The motor endings in the tongue were also fairly well conserved by the artificial circulation.

The œsophagus remains irritable, both to direct stimulation and to stimulation of the vago-sympathetic, for long periods of time under the influence of artificial circulating fluids. Stimulation of the vago-sympathetic may also affect the œsophagus at a time when there is no effect on the eye, although the eyelid responds readily to direct stimulation. This difference in the reaction of the two structures may be due to the interpolation of a synapse on the path to the eye, while there is, so far as we are aware, no synapse on

the path to the œsophagus. Instances of such phenomena have been given elsewhere. In one experiment, Number 11 (March 1, 1905), the œsophagus about two inches above the heart was observed to beat with almost the same rhythm as the auricles. We do not know the cause of these rhythmical contractions, but offer the suggestion that they might have been due to the action current of the heart. As is well known, the action current of the heart may, under certain conditions, excite the phrenic nerve and cause rhythmical contractions of the diaphragm which are synchronous with the heart beats.[18]

The Comparative Argument for the Automaticity of the Respiratory Mechanism.—Additional evidence of the automatic or reflex nature of the origin of cardio-inhibitory and vasomotor tone and of the respiratory movements, as we mentioned above, may be obtained from a comparative study of these mechanisms with that for deglutition. We have pointed out elsewhere that the synapse is a weak link in the nervous reflex arc. So far as we can see, there is no apparent reason why two such arcs as that through the respiratory center and that through the swallowing center should not be resuscitated at approximately the same time. As Marckwald[19] has shown, there is a very intimate physiological, and probably anatomical, connection between these two centers. If respiration were reflex, as swallowing so evidently is, we should expect a very close correspondence in the time of resuscitation of these two mechanisms. But when we look for such correspondence in time, we do not find it. On the contrary, as will appear from the various protocols quoted and from Table II, we find that respiration returns considerably earlier in the resuscitation than swallowing does. The most obvious conclusion is that respiration occurs in the absence of afferent impulses. The time at which stimulation of the afferent nerves begins to affect respiration corresponds much more closely with the time at which swallowing first occurs.

The vasomotor and swallowing mechanisms may be compared in a similar way, and again we conclude, from the early appearance of vasomotor tone, and the relatively late return of the influence of

[18] Stewart and Pike, *Amer. Jour. of Physiol.*, 1907, xix, 339.
[19] Marckwald, *Zeit. f. Biol.*, 1888, xxv, 1.

afferent nerves upon the blood pressure, that there is a very marked automatic element in the origin of the vasomotor tone. Very probably the circulation of the blood to the different organs according to their needs is brought about reflexly, but it seems to us that the height of the general systemic blood pressure may well be due to an automatic mechanism.

When we compare the time of the resuscitation of the cardiac centers with that of the swallowing centers, the results, and therefore the conclusions also, are somewhat different. The respiration becomes established, and the blood pressure reaches a considerable height—perhaps its maximum, before reflex cardiac effects appear. Then, suddenly, the reflex arc is again integrated and the heart becomes visibly affected by afferent impulses to the bulbar centers. In point of time, cardio-inhibition appears much nearer the return of swallowing than do the other two functions. We conclude, therefore, that cardio-inhibition and acceleration are very largely reflex in origin.

When we study the relative order of failure of these four functions during the occlusion period, we find further evidence in favor of these conclusions. The march of events is so rapid, and certain other conditions, to be mentioned presently, which enter in here, complicate things so much that this evidence is probably not so trustworthy as that drawn from observations during the period of resuscitation. The swallowing movements fail first, then the cardiac impulses and finally the respiration and vasomotor tone. We might reasonably expect therefore that, since the synapse is the weak link, the reflexes would fail first, and the automatic functions persist longer.

The only disturbing factor is that entering into the deportment of the heart, since cardiac acceleration persists longer than we would expect a pure reflex to do. It is possible, but perhaps not probable, that the mere asphyxiation of the cells of origin of the inhibitory nerves serves to excite them until they succumb, at which time the accelerators become active, as we have previously pointed out.[20] It is, however, noteworthy that even the cardio-acceleration fails before respiration, and it has not been shown that the cardiac

[20] Stewart and Pike, *Amer. Jour. of Physiol.*, 1907, xix, 349.

centers ordinarily remain active when afferent impulses are excluded, without, at the same time, interfering with the afferent paths.

Bearing in mind all of the phenomena of occlusion and resuscitation, we conclude that respiration and vasomotor tone are, at their inception in the resuscitation period, almost or quite automatic; later, afferent impulses begin to affect them; the cardiac centers, on the contrary, are, under normal conditions, almost or quite dependent upon afferent impulses for their activity.

III. THE RESUSCITATION OF THE HIGHER NERVOUS MECHANISMS.

The Return of the Eye Reflexes.—The relative time of the failure of the eye reflexes, as compared with the respiration, during the occlusion period, and of their return in the resuscitation period have been given in detail in another paper, and will not be dwelt upon at length here. There are, however, certain new facts in the action of the cervical sympathetic upon the pupil that we wish to present in this paper.

The artificial circulation of fluids through the head does not, as a rule, long maintain the integrity of the sympathetic endings about the pupil. This is shown in the various protocols already cited in the first of these studies. Again, the cervical sympathetic, when stimulated, may fail to affect the pupil, but the lachrymal gland will secrete, apparently in response to the stimulation.

In one experiment (12) in which the head arteries were occluded for several short periods, and a mixture of fresh defibrinated blood and Locke's solution circulated through the head later, stimulation of the left vago-sympathetic nerve, in continuity, caused enormous dilation of the left pupil, with bulging of the eye and retraction of the nictitating membrane. At the end of one minute, the left pupil was still widely dilated, and the right pupil was also dilated, although not as much as the left. Twenty-five minutes later, stimulation of the left vago-sympathetic gave the same effect on the left eye as before. After an interval of a few seconds, the right pupil also enlarged, the lateral half dilating much more than the medial half. Two minutes later, the left vago-sympathetic was again stimulated. Some dilation occurred in the left pupil, which had remained much dilated since the previous stimulation, but there was no effect on the right pupil, which had remained the same size. Very shortly afterward—three or four minutes—both pupils became totally insensible to stimulation of the cervical sympathetic.

From the protocols given in the first of these studies, we see that the œsophagus may respond to stimulation of the vago-sympathetic trunk in continuity after the pupil fails to respond, although the pupil may still respond to direct stimulation in some instances.

In Experiment 13 (April 3, 1905) the left pupil remained much narrower than the right for a long time in the resuscitation period. Three and one fourth hours after release, following an occlusion of 50 minutes, neither section nor stimulation of the left vago-sympathetic caused any change in the left pupil, which remained contracted. The right pupil was at maximal dilation.

We have supposed there might be a synapse on the sympathetic pathway to the eye, which broke down, under the adverse influences of anæmia and the artificially circulated fluids, sooner than a direct pathway free from synapses.

We have observed, also, that, when the eyes are widely opened and bulging, and the cornea hard, probably indicating a high intra-ocular pressure, the stimulation of the cervical sympathetic may not cause maximum dilation of the pupil, and that whatever dilation occurs disappears soon after the cessation of stimulation, the pupil quickly returning to normal.

There has been much discussion among authors as to whether the respiratory or the pupillo-motor center is the more resistant to cerebral anæmia, and which was the first to be resuscitated. Hayem[21] states definitely that the respiratory center is the last of the cerebral centers to fail in death from hemorrhage. We have found that the respiration returns in cats before the pupils are contracted. Herlitzka,[22] in discussing some of D'Halluin's[23] criteria of resuscitation, states that contraction of the pupil may be a purely hydraulic phenomenon[24] depending upon pressure factors alone, and is not, therefore, an accurate index of the functional activity of the pupillo-motor center. In the absence of all other cerebral functions the contraction or dilation of the pupil may not be a trustworthy sign of functional activity, but if other centers are active, we see no reason why the state of contraction of the pupils should

[21] Hayem, *loc. cit.*
[22] Herlitzka, *Arch. ital. de biol.*, 1905, xliv, 93.
[23] D'Halluin, *loc. cit.*
[24] Mosso, cited by Herlitzka, *loc. cit.*

not be regarded as a valid index of the functional activity of the pupillo-motor center. Indeed, we have experimental evidence that the state of contraction of the pupil does not always depend upon blood pressure alone. We have pointed out, in our first paper, the difficulty of distinguishing between the effects due to the cerebral center and those due to sympathetic influences and will not enlarge upon them here.

The mere contraction of the pupil, as it occurs in the return of cerebral function, must be carefully distinguished from the contraction and relaxation due to changes in the intensity of the light. The pupils may be contracted in the resuscitation period, and the light reflex absent. During the succeeding days the pupils may be wide, especially during the spasms, and the light reflex present, in some degree at least.

The widening of the pupils during spasms, as we have stated elsewhere, is an almost, or even quite, constant occurrence. The dilation may not appear as soon as the spasms begin, but some hours after, and is always plainly evident in those animals which are kept alive on the day following the operation.

In Experiment 14 (May 13, 1905), for example, in which the head arteries were occluded for one hour, permanent extensor spasms of the forelimbs were noticed five hours and 46 minutes after release of the head vessels. Fairly strong spasms of the forelimbs began six hours after release, and increased in severity as time elapsed. It was not until eight hours and 20 minutes after release that the pupils were observed to dilate during the spasms, which, at that time, were of considerable severity.

We have mentioned in another place the fact that the cornea becomes sunken and furrowed during the period of anæmia, if the occlusion is at all prolonged, and that the cornea may again become smooth and firm in the resuscitation period. The time in minutes after occlusion at which the corneal tension begins to decrease, and the time in minutes after release when the cornea again becomes firm, are shown in Table II, which gives also the length of the

TABLE II.

Length of Period of Occlusion in Minutes	Minutes after Occlusion when Tension Begins to Lessen.	Minutes after Restoration of Circulation when Tension Returns.
31	3 min. 50 sec.	21 min. 30 sec.
10	7 min. cornea furrowed	18 min. 30 sec.
15	———	32 min.
8	30 sec.	5 min. 40 sec.

occlusion period. The effect of intraocular tension upon the response of the pupil to stimulation of the cervical sympathetic has already been mentioned.

The intra-ocular tension may be maintained for a time, or even restored in rare instances, by a good circulation of fresh defibrinated blood through the head end of an animal.

The Temperature of the Animals in the Post-Anæmic Period.—The question arises whether the temperature of the animal remains the same or whether the heat regulating mechanism, sharing the general derangement and sometimes apparent hyperactivity of the other nervous mechanisms, maintains an abnormally high temperature for a time.

At the conclusion of the operation, and after the respiration has returned so that the animal is able to breathe spontaneously, the temperature, taken in the rectum, is often subnormal. The temperature as measured at varying intervals during the post-anæmic period is given in Table III.

The temperature immediately before occlusion of the cerebral arteries was sometimes subnormal, *e. g.*, 36° C., particularly if the dissection of the vessels had been tedious, but was always markedly below normal at the end of occlusion, falling to 32° C. in one instance. A fall of 0.6° C. occurred during an occlusion of ten minutes. In the cases where marked cerebral injury resulted from the occlusion, the temperature often fell one or two degrees after the release of the cerebral arteries, but subsequently rose again. In a case of severe convulsions the temperature was 39.7° C. on the day after the operation. In another case where no violent convulsions were observed after the first few hours, the temperature was 32° on the day after the operation. Another animal which recovered without abnormal symptoms had a temperature of 38.4° C. on the second day. In some instances where the temperature fell very low, the animal was put in a covered box which could be heated by a burner beneath it. Sometimes a rise of temperature followed this procedure, the rise continuing after extinguishing the flame or removing the animal from the box, and reaching a point somewhat above normal. Putting in the ice chest, primarily for the purpose of controlling the spasms, caused a fall of temperature,

TABLE III.

Showing the length of the occlusion period, and the temperature of the animals at varying periods after the release of the cerebral arteries.

Number of Experiment.	Length of Occlusion.	Temperature (Rectal).	Time after Release.
I.	60 minutes 30 seconds	32° C.	4 min.
		31	24 "
		30.5	37 "
		30.4	47 "
		30	1 hr.
	Artificial heat	29.8	1 " 27 "
		29.5	1 " 42 "
		30	2 "
		30.30	2 " 8 "
		31.2	2 " 19 "
		32.8	2 " 43 "
	No more heat	33.5	2 " 58 "
		33.8	3 " 33 "
	Artificial heat	33.5	5 " 45 "
		33.5	5 " 58 "
	Burner turned out	33.5	6 " 4 "
		34.2	6 " 58 "
		34.4	7 " 6 "
		Put in ice chest	
		32	7 " 33 "
	Not on ice	32	7 " 47 "
		32.2	8 " 5 "
	In ice chest		
		30.4	8 " 38 "
		30.4	8 " 56 "
		30.4	9 " 8 "
		30.7	9 " 33 "
		32.4	12 " 23 "
		Death	15 " 8 "
II.	26 minutes		
		33.3	5 "
		32	6 "
		33.5	21 "
		33	34 "
		31	4 " 37 "
		32	20 " 50 "
		32.9	26 " 20 "
III.	10 minutes 7 seconds	35.4	During occlusion
		35.2	5 "
		35	14 "
		34	1 " 24 "
		39.7	21 " 24 "
IV.			
		34	30 "
		37	20 "
V.	45 minutes		
		36.5	At release
		36	14 "
		35.3	26 "
		34.8	38 "
		34.6	51 "
		34.3	1 " 5 "
		33.4	1 " 53 "
		33.3	2 " 54 "

the fall sometimes continuing after the removal from the ice. In general, the temperature regulating mechanism of the animal suffers along with the other cerebral mechanisms, the extent of the variations of the temperature depending, in a somewhat general way, upon the severity of the general effects of anæmia. If the animal recovers its other cerebral functions the temperature regulation, as a rule, again becomes normal.

Von Bechterew[25] and others were led, from a consideration of clinical evidence, to suspect the existence of a cortical center for the secretion of sweat. In a recent paper, von Bechterew[26] gives the experimental evidence for the existence of such a center. On the basis of this work we may explain the cause of the sweating in Green's[27] case by supposing that the center for the secretion of sweat, like many other cortical centers, is not acting in a normal manner, or may even be hyperexcitable, as the cortical motor centers apparently are. The conditions in cats are not so easy of observation, and we have no constant results on this phase of the subject. In most instances, in which attention was directed to this point, the pads of the feet were moist.

Some glycosuria is always present in animals which live more than a few hours. This is not due to the anæsthetic alone, as was shown by control experiments. It is possible that the injury or excitation of the medullary "diabetic center," similar to that which produces puncture glycosuria, may explain the appearance of dextrose in the urine. The experiments of von Bechterew showed that stimulation of a particular area of the motor cortex in the dog caused an increased flow of urine, and, frequently also, glycosuria. The derangement of such a cortical mechanism in the cat would explain the glycosuria so constantly noted.

The Resuscitation of the Cerebral Motor Cortex.—The activity of the motor cortex is not well maintained by artificial circulation of defibrinated blood or other fluids, as is shown by the protocols of the experiments already quoted. Moreover, the white matter, *e. g.*, the fibers of the corona radiata, soon loses its excitability

[25] v. Bechterew, *Arch. f. Physiol.*, 1905, 297.
[26] v. Bechterew, *loc. cit.*
[27] Green, *loc. cit.*

under the influence of the artificial circulatory fluids, as shown in Experiment 10. The cortex is inexcitable during the period of anæmia, and may fail to recover after the normal circulation is reëstablished.

In Experiment 15 (March 4, 1905) the head arteries of an adult cat were occluded for ten minutes. The pupils slowly contracted after release of the head vessels, but began to dilate again about one hour after release. No corneal or other reflex ever returned. Shortly after the two pupils began to dilate (62 minutes after release) about 100 c.c. of a mixture of fresh defibrinated blood and Locke's solution (45 c.c. blood diluted to 275 c.c.) was injected into the aorta under a pressure of 100 mm. of mercury to increase the volume of circulating fluid. The pupils became narrow in nine minutes after the injection was begun. Three minutes later, stimulation of the left vago-sympathetic produced dilation of the left pupil, retraction of the nictitating membrane and bulging of the eye. The dilation of the pupil disappeared almost as soon as the stimulation was stopped, but the bulging of the eye persisted a little time. Eighteen minutes after starting the injection, gasping movements occurred, increased in strength and persisted thirteen minutes. At the end of this interval, 31 minutes after starting the injection, the left pupil was dilating and the blood pressure in the carotid was low. About 30 c.c. of the blood mixture was now injected, and respiratory movements came back almost at once, but grew feebler in four minutes. Marked spasms of the face muscles occurred. Thirty-six minutes after starting the first injection a third injection of the blood mixture was begun. Artificial respiration was suspended for 40 seconds, and then started again. The respiratory gasps began almost immediately afterward. At this time, 41 minutes after the first injection, the animal puckered up its face and closed its eyes tightly. The pupils dilated greatly, and both respiratory gasps and facial spasms ceased in one and one half minutes. A fourth injection was begun 65 minutes after the first. The pupils again contracted somewhat, only to dilate again, and nasal and lachrymal secretion appeared. A fifth injection occurred 72 minutes after the first, and again the pupils contracted. At this time, stimulation of the left vago-sympathetic caused dilation of the pupil. Eighty-one minutes from the beginning of the first injection, the skull was trephined and the left motor center stimulated. There were no movements of any kind. The cortex was then excised and the corona radiata stimulated, with the same result as for the cortex. Seven minutes later, the experiment was stopped. There was some twitching of the right eyebrow at this time, and the heart was still in good condition.

In Experiment 16, a part of the protocol of which is here cited, the motor cortex was excitable to direct stimulation fifty minutes after starting the heart.

Experiment 16 (March 18, 1905). Cat. Ether. Tube in larynx, artificial respiration.

11:28 A. M. Occluded head arteries.

11:40:45. Released head arteries. Soon after this, animal stopped breathing. Opened thorax and massaged heart directly.

12:05 P. M. Heart started again.

12:57. Pupils well contracted. No light reflex but corneal reflex is present.

12:57:30. Light reflex back. Swallowing. Marked lachrymal secretion.

1:02. Pupils of normal size. No reaction of animal to loud sounds produced by clapping hands. Shoulders and head move when board is sharply struck.

1:09. Touching interior of ear causes movements of eyelid on same side. These are produced especially well by flicking the ear with the finger. No movements of eyelids on opposite side.

1:22. Moved head on whistling in ear but not on blowing into it, though blowing caused lid movements.

1:45. Put ammonia in the nostrils. No effect. Put ammonia in the mouth. Strong movement of head and neck and some movements of forelimbs. Trephined skull.

1:55. Stimulated motor cortex. Got jaw movements of opposite sides. No other movements except perhaps slight movement of opposite forelimb. As soon as the skull was opened, occasioning some hemorrhage, deep regular spontaneous respiratory movements began, involving head, neck and chest down to diaphragm. It was not observed whether the diaphragm took part. These movements were much more effective for respiration than the previous gasping respiratory movements.

Similar results have been obtained by Scheven[28] on rabbits. This observer found that the white matter of the central nervous system was more resistant to anæmia than the gray matter. Stefani and Cavazzani[29] found that the rabbits' peripheral nerves would retain their conductivity for afferent impulses up to ten minutes after being deprived of their blood supply.

We have previously pointed out[30] that the convulsions occurring during the resuscitation period after cerebral anæmia[31] are not necessarily due to the motor cortex, since the same phenomena occur in animals in which the brain has been divided at about the level of the roots of origin of the fifth nerve.

Micturition sometimes occurs during these convulsions, with the anatomical connections intact. While it is possible that the expulsion of the vesical contents is due to the spasm of the abdominal muscles, there is also the possibility of involvement of the cortical motor center for the bladder.

[28] Scheven, *Arch. f. Psychiatrie,* 1904, xxxviii, 926; *ibid.,* 1904, xxxix, 169.

[29] Stefani and Cavazzani, *Mem. letta all' academia medico-chirurg. di Ferrara,* 1888, cited by Scheven.

[30] Stewart and Pike, *Amer. Jour. of Physiol.,* 1907, xx, 72.

[31] Stewart, Guthrie, Burns and Pike, *Jour. of Exper. Med.,* 1906, viii, 307.

Mewing, indicating recovery of the cortical area for phonation, has been observed twenty-two and one half minutes after release from an occlusion of five minutes. The light reflex was well marked at this time, and the pupils were of normal size. The spasms were marked. The mournful mewing was evidence of a considerable degree of cortical activity. In another experiment, of fifteen minutes occlusion, the spasms were of marked severity six hours after release. The cat uttered a peculiar "yowl" from time to time during the spasms, and particularly during the latter stage of a spasm. This cry may have been from the corpora quadrigemina,[32] and not from the cortex. The cat was found dead fourteen hours later.

Consciousness, in some degree, has been observed twenty-five minutes after release from an occlusion of nine and five sixths minutes. There was no light reflex present at this time, but the tail was wagging. Flicking the fore paws caused strong gasping movements. Consciousness, and the reflexes have persisted throughout an imperfect occlusion of eighteen and one half minutes, followed, thirty-five minutes later, by a second imperfect occlusion of thirty minutes. The fore limbs, particularly the left, were weak until the animal's death eight days later, and straddled out from the body in walking. A spastic gait is often observed when the animals begin to walk about after recovery from the operation.

Voluntary movements of the head, neck, shoulders and fore limbs, but no corneal reflex, and respiratory movements involving the muscles down to the shoulders, have been observed eight minutes after release from an occlusion of six minutes. Voluntary change of position was observed in another animal three and one half hours after release from an occlusion of thirty-one minutes. In another case, no voluntary movements ever returned, even twelve hours after release from an occlusion of forty-five minutes, although the circulation to the head was good all of the time.

Continuous sleep, with tightly closed eyes, was observed twenty hours after release from an occlusion of five and five sixths minutes following an incomplete occlusion of nine and one half minutes.

[32] Ferrier, Functions of the Brain, 2d edition, New York, 1886, p. 166.

The rectal temperature was 38.7° C. The clonic spasms were entirely gone, and did not appear on stimulation. The respiration was thirty-three a minute, and regular. The light and corneal reflexes were well marked. The animal swallowed salt solution placed in the mouth, and tickling the ear caused the ordinary movements of it.

The Senses after Recovery from Anæmia.—Sight is often apparently normal after cerebral anæmia, but apparent total blindness has also been met with. Blindness did not occur immediately, but developed within a week or ten days after occlusion. Strangely enough, the light reflex appeared to be present in some degree. The corneal reflex still remained, for the eyelids were closed when the eyeball was touched. The pupils were often wide and staring, but were sometimes seen to be narrowed in bright light. The location of the lesion, whether in the retina or in the cerebral center, and its nature are unknown.

We have observed wide and staring pupils in animals whose sense of sight was still present. The nature of the impression made on the disordered brain is a matter of conjecture. The animals howled when anyone came into view, but showed neither fear nor affection. The vision often becomes apparently normal so far as we were able to determine by our tests. In one experiment, the sense of sight had evidently returned three hours and fifty minutes after release from an occlusion of nine minutes and fifty seconds.

Hearing.—Like sight, the auditory sensation shows varying degrees of recovery. After anæmia and during the period of convulsions, there is often apparently increased sensitiveness to slight sounds. The ticking of a watch is often sufficient to cause convulsions, all other stimuli being excluded. In favorable cases, the return of hearing is apparently complete. Total deafness, as a result of cerebral anæmia is rather doubtful, but deafness to ordinary sounds is well established, for example, calling, and the mewing of kittens were unnoticed. A loud, sharp report near the ear usually attracted some attention. The location and nature of the lesion are unknown.

Hearing returns somewhat earlier in the resuscitation period

than sight. In one experiment, in which the heart was started by massage after a stoppage of fifteen to twenty minutes, loud sounds caused no reaction one hour after the heart began to beat. One hour and twenty minutes after starting the heart, the head moved on whistling in the ear, but not on blowing into it, although this blowing caused eye movements. Again in another experiment in which the heart stopped for about ten minutes after an occlusion of six minutes, the cat moved on striking the board sharply fifty minutes after starting the heart, but not on calling or clapping the hands. Hearing had probably not returned in this last experiment.

The recognition of sounds returns somewhat later than the mere audition. In the last experiment in the preceding section (in which there was an occlusion of nine and five sixths minutes), the animal recognized sounds, *e. g.*, "pussy," three hours and twenty minutes after the release of the head arteries. Thirty minutes later there was evidence of sight. In another experiment, the sense of hearing was apparently abnormally acute fifty minutes after release after an occlusion of three and one third minutes, the animal starting at any sound, and going into tonic extensor spasms. Two hours later, the cat was sitting in the normal position of a couchant cat, but with the head turned sharply to the right. A loud sound caused it to change its position, the animal lying on its belly with its head straight in front.

The results on *taste* and *smell* are not so definite. Ordinarily the animals eat well, and manifest a preference for certain kinds of food. Food may be taken when the animal is blind and deaf. Milk held near the nose may not be lapped unless the nose is actually touched with it, but, once tasted, is eagerly eaten.

Touch.—After the exaggerated sensibility to touch of the first few hours or days following anæmia, the sense of touch becomes apparently normal in animals which show otherwise favorable symptoms. There is the normal response to stroking the fur. Even a blind and deaf cat showed this response and would often mew when stroked. We believe it is a response to touch as a sensation rather than the response of a spinal animal to a stimulus. The reflex response to tickling the ears was always observed if a

sufficient time was allowed to elapse after anæmia. Pain and temperature sensations were present in the cats which recovered well otherwise, but the responses to these stimuli could not always be interpreted in animals which suffered apparent loss of some of the other senses.

The Return of the Mental Processes.—This is perhaps the most interesting of all the phases of the resuscitation of the brain, and a phase which can be studied in detail by the clinical observer alone. Animals may be watched in the laboratory, and may manifest all the functions normal to the ordinary animal, but we are unable to tell whether the mental processes are completely restored.

So far as we are able to judge from the deportment of the animals, all the mental faculties may return after short periods of occlusion (eight minutes). The animals observed showed no noticeable change in deportment. The responses to calling and stroking were normal. A white rat allowed to run in front of one cat was at once pounced upon, and was rescued only with difficulty. On the application of a non-irritating antiseptic solution to the skin lesions which developed later, the cat showed the usual aversion to water. The general results in this case were decidedly encouraging. We have other examples of apparently complete return of the mental processes after occlusions of six minutes, seven and one half minutes, nine and five sixths minutes and sixteen and one half minutes. In this last experiment, however, we doubt the totality of the anæmia produced.

Such a favorable result does not always follow. After an occlusion of ten minutes, we have seen apparently the total loss of intelligence. We have also observed an apparent insanity along with the return of the bodily functions.

In a previous paper we pointed out that strychnine, either had no noticeable effect on the previously anæmic cord or else paralyzed it, when injected in very small quantities, before affecting the normal cord. In looking over our experiments, we find that only one cat survived the subcutaneous injection of strychnine, the rest all dying within a few hours at most. The action of strychnine in excess is to paralyze the normal cord. Since the previously anæmic area may reasonably be supposed to have a lowered vitality

and a diminished resistance to external influences, it is possible, and, in the light of our experiments, very probable that the therapeutic dose of strychnine may have an injurious effect instead of a beneficial one.

The Pilo-motor Mechanism.—Although it is probably not to be considered as exclusively under the control of the higher centers, the pilo-motor mechanism may be discussed here. Movements of the hair of the cheeks, and particularly of the vibrissæ, are not infrequent in the resuscitation period.

For example, in Experiment 17 (May 27, 1905), 45 minutes after release, following an occlusion of 45 minutes, there was constant twitching of the hair of the throat and cheeks, and of the vibrissæ. At this time the respiratory gasps were occurring at intervals of 18 seconds, and there were clonic movements of the forelimbs, with a response to striking or pinching the limb on the same side stimulated. The forelimb reflexes did not cross.

In Experiment 18, nearly five hours from the release of an occlusion of 51 minutes, the hairs on the tail were erected one minute after stopping artificial respiration (natural respiration had not returned). A second short period of asphyxia three minutes later was followed by the same result. Erection of the hairs on the tail and back has been observed during the spasms. In Experiment 14, the hairs of the tail and back were erected continuously (indicating tonic pilo-motor spasms) eight hours and 40 minutes after release from an occlusion of 60 minutes. At this time the pupils were beginning to dilate during the spasms.

CONCLUSIONS.

The experiments on cerebral anæmia have enabled us to duplicate, by an entirely different method, many of the results obtained by anatomical division or removal of parts of the central nervous system. In some respects the method of anæmia permits of greater precision than the method of division or excision, and avoids, in great measure, the disturbances due to the wound and to the hemorrhage caused by the latter method. The method of general anæmia, as Couty[33] pointed out long ago, leaves something to be desired in the matter of exact localization, but this objection may be met, in some degree at least, by appropriate methods of investigation. It is desirable that the results obtained by the method of section should be duplicated by some other method in order to eliminate as much as possible the effects due to the irritation produced by the anatomical lesion.

[33] Couty, *loc. cit.*, p. 754.

Our results show, as we believe, that, of the bulbar mechanisms studied, the respiratory is the most automatic, the vasomotor in part automatic, and the cardiac like the swallowing mechanism, almost wholly dependent upon afferent impulses for the arousal and discharge of its normal activity.

The eye reflexes return during the resuscitation period in the animals in which the cerebral anæmia has not been too prolonged. The motor cortex loses its excitability during anæmia, but may regain it after the reëstablishment of the circulation. The pilomotor mechanism is disturbed during the spasms which occur at a certain stage in the resuscitation. The temperature falls during the occlusion period, but rises again, often to far above normal, in the days following the anæmia. So many disturbing factors, such as the violent muscular contractions during spasms, enter into the problem that it is impossible to say that there is an actual disturbance of the temperature regulating mechanism although we are inclined to believe that this is the case.

All the senses return, following cerebral anæmia, but sight and hearing may afterwards fail without causing the death of the animal. The mental processes may return without any apparent deficiency, if the period of anæmia has been short. After longer occlusion, apparent insanity has been seen, and in one case, apparent total loss of mental processes occurred.

The reflex excitability of the cord returns rather early in the resuscitation period. Reflexes from the anterior part of the cord first involve muscles on the same side as the stimulus, and later cross to involve muscles of the opposite side. The spinal cord sometimes falls into much the same condition as that following spinal transection, and the scratch reflex appears. Spinal transection, when these reflexes have appeared, does not produce shock. Practically all phenomena of spinal shock may be reproduced without section of the cord. We conclude, therefore, that spinal shock is due more to the cutting off of the reflex pathways through the higher centers of the nervous system than to the stimulation of inhibitory fibers by the anæmia.[34]

[34] Pike, Guthrie and Stewart, *Amer. Jour. of Physiol.*, 1908, xxi, 371.