Archives of Neurology and Psychiatry (1943) 50 : 510-528

ACUTE ARREST OF CEREBRAL CIRCULATION IN MAN

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Numerous investigations have been concerned with the effects of acute arrest of cerebral circulation in animals. The earlier workers [1] studied the effects of ligation of the cerebral arteries. More recently, observations have been made on the effects of temporary occlusion of the chief cerebral arteries [2] and of temporary cessation of the heart beat.[3] Using the method of occlusion of the chief cerebral arteries, Sugar and Gerard [4] measured the survival time for different regions of the cat brain by the persistence of spontaneous action potentials. A careful study of the changes in function and structure of the brain of the cat resulting from temporary occlusion of the pulmonary artery was reported on by Weinberger, Gibbon and Gibbon.[5] These methods involved one or another of the following complications: anesthesia; surgical procedures at the time of arrest of circulation in the brain; incomplete arrest of circulation as a result of failure to occlude the anterior spinal artery; arrest of circulation in vital organs outside the central nervous system, and difficulty of determination of the exact moment of cessation of the heart beat.

For quantitative study a technic was utilized which produced sudden complete arrest of blood flow in the brain of the unanesthetized animal without the per-

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1. Cooper, A.: Some Experiments and Observations on Tying the Carotid and Vertebral Arteries, Guy's Hosp. Rep. **1**:465, 1836. Kussmaul and Tenner: Untersuchungen über Ursprung und Wesen der fallsuchartigen Zuckungen, Untersuch. z. Naturl. d. Mensch. u. d. Thiere **3**:3, 1857. Hill, L.: On Cerebral Anemia and the Effects Which Follow Ligation of the Cerebral Arteries, Phil. Tr. Roy. Soc., London, s.B **193**:69, 1900.

2. Pike, F. H.; Guthrie, C. C., and Stewart, G. N.: Studies in Resuscitation: IV. The Return of Function in the Central Nervous System After Temporary Cerebral Anemia, J. Exper. Med. **10**:490, 1908. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

3. Boehm, R.: Ueber Wiederbelebung nach Vergiftungen und Asphyxie, Arch. f. exper. Path. u. Pharmakol. **8**:68, 1877. Batelli, F.: Le rétablissement des fonctions du coeur et du système nerveux central après l'anémie totale, J. de physiol. et de path. gén. **2**:443, 1900. Crile, G., and Dolley, D. H.: On the Effects of Complete Anemia of the Central Nervous System in Dogs Resuscitated After Relative Death, J. Exper. Med. **10**:782, 1908. Heymans, C.; Bouckaert, J. J.; Jourdan, F.; Nowak, S. J. G., and Farber, S.: Survival and Revival of Nerve Centers Following Acute Anemia, Arch. Neurol. & Psychiat. **38**:304 (Aug.) 1937.

4. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938.

5. (*a*) Weinberger, L. M.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation to the Central Nervous System: I. Physiologic Effects, Arch. Neurol. & Psychiat. **43**:615 (April) 1940. (*b*) II. Pathologic Effects, ibid. **43**:961 (May) 1940.

formance of a surgical procedure at the time and without deprivation of other organs of blood or oxygen. This was accomplished [6] by the use of a cervical pressure cuff in dogs at a pressure of 600 mm. of mercury following a preliminary cervical laminectomy. With this method, the corneal reflex disappeared within ten seconds and spontaneous respiration ceased in twenty to thirty seconds. The essential basis for this rapid loss of function was lack of oxygen for the neurons. In normal adult dogs of either sex, periods of arrest of circulation in the brain of six minutes or less, while producing severe functional changes for a time, were invariably followed by apparently complete functional recovery. On the other hand, arrest of circulation in the brain for longer than six minutes uniformly resulted in permanent coma, due to functional decortication. Damage to the brain was sharply localized in specific sensitive areas and was confined to the nerve cells.[7] The course of functional recovery was essentially the same as had been reported in cases of acute arrest of cerebral circulation in man by hanging.[8] The brain of the very young animal was much more resistant to arrest of blood flow than that of the adult [9] while pregnancy or lactation increased the sensitivity of the brain to temporary arrest of circulation.[10]

Relatively little study has been made of the effects of acute arrest of blood flow in the human brain. The most significant contributions in this field have been those of the Harvard group: namely, the studies on the hypersensitive carotid sinus reflex and carotid sinus syncope,[11] on the relation of the oxygen content of blood in the internal jugular vein to loss of consciousness [12] and on the electroencephalographic pattern associated with carotid sinus syncope.[13] Other investigators [14] have described the clinical syndrome produced by short periods of acute anoxia induced by breathing gas mixtures of low oxygen content. Of considerable interest

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6. (*a*) Kabat, H., and Dennis, C.: Decerebration in the Dog by Complete Temporary Anemia of the Brain, Proc. Soc. Exper. Biol. & Med. **38**:864, 1938. (*b*) Kabat, H.; Dennis, C., and Baker, A. B.: Recovery of Function Following Arrest of the Brain Circulation, Am. J. Physiol. **132**:737, 1941.

7. (*a*) Kabat, H., and Schadewald, M.: The Relative Susceptibility of the Synaptic Terminals and of the Perikaryon to Arrest of the Circulation of the Brain, Am. J. Path. **17**:833, 1941. (*b*) Kabat, H., and Grenell, R. G.: Specificity of Localization of Neuronal Injury Following Arrest of Brain Circulation, Anat. Rec. **82**:33, 1942.

8. Strauss, H.: Strangulationsfolgen und Hirnstamm, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:363, 1931. Salinger, F., and Jacobsohn, H.: Psychische Störung nach Strangulationsversuch, ibid. **110**:372, 1927. Kabat, Dennis and Baker.[6b]

9. Kabat, H.: The Greater Resistance of Very Young Animals to Arrest of the Brain Circulation, Am. J. Physiol. **130**:588, 1940.

10. Kabat, H.: The Influence of Pregnancy and Lactation on the Susceptibility to Arrest of the Brain Circulation, Proc. Soc. Exper. Biol. & Med. **44**:23, 1940.

11. (*a*) Weiss, S., and Baker, J. P.: The Carotid Sinus in Health and Disease: Its Role in the Causation of Fainting and Convulsions, Medicine **12**:297, 1933. (*b*) Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, ibid. **14**:377, 1935.

12. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: (*a*) Relationship of Unconsciousness to Cerebral Blood Flow and to Anoxemia, Arch. Neurol. & Psychiat. **34**:1001, 1935; (*b*) The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:277, 1938.

13. Forster, F. M.; Roseman, E., and Gibbs, F. A.: Electroencephalogram Accompanying Hyperactive Carotid Sinus Reflex and Orthostatic Syncope, Arch. Neurol. & Psychiat. **48**: 957 (Dec.) 1942.

14. Fraser, R., and Reitmann, F.: A Clinical Study of the Effects of Short Periods of Severe Anoxia with Special Reference to the Mechanism of Action of Cardiazol Shock, J. Neurol. & Psychiat. **2**:125, 1939.

are the studies on recovery from attempted suicide by hanging [15] and resuscitation after cardiac arrest.[16]

All these investigations on acute arrest of circulation in the human brain were limited almost entirely to patients with various disorders, such as hypersensitive carotid sinus reflex, orthostatic hypotension and Stokes-Adams disease. Many of these patients were in the older age group and suffered from arteriosclerosis, hypertension or heart disease. The experiments were difficult to control, and much variation was noted, which limited the accuracy of quantitative observations. Furthermore, there is reason to believe [13] that the syncope resulting from stimulation of a hypersensitive carotid sinus reflex is complex and bears a closer relation to an epileptiform seizure than to syncope from cerebral anemia.

In order to study the effect of acute cerebral anoxia in man, a new technic was devised, which used the Kabat-Rossen-Anderson apparatus. This procedure is essentially an adaptation to the human subject of the method devised by one of us [6] for producing arrest of cerebral circulation by means of a cervical pressure cuff. Acute arrest of circulation in the human brain was studied in 11 schizophrenic patients and in 126 normal young male subjects. No deleterious effects were observed from repeated tests on these subjects.

ANATOMY AND PHYSIOLOGY

Arterial blood is supplied to the human brain chiefly through the internal carotid and the vertebral arteries, but to some extent by anastomotic connections of branches of the external carotid and the subclavian artery. In addition, some blood reaches the brain through the small spinal arteries.

The common carotid artery is readily occluded by external cervical pressure, blood flow to the brain through the internal carotid artery and branches of the external carotid artery being thereby eliminated. The ascending branches of the subclavian artery, with the exception of the vertebral artery, are also readily occluded by a circular cervical pressure cuff.

The vertebral artery is a branch of the first part of the subclavian artery. In the lower portion of the neck, the first part of the vertebral artery runs upward and backward between the scalenus anticus and the longus colli muscle to enter the foramen in the transverse process of the sixth cervical vertebra. The second part of the vertebral artery passes upward, entering the series of foramens in the transverse processes of the vertebrae from the sixth cervical to the atlas. The third part of the vertebral artery enters the skull and joins the vertebral artery of the opposite side at the base of the brain to form the basilar artery. It is impossible to occlude the third part of the vertebral artery by cervical pressure. The second portion is difficult to occlude by external pressure because the artery can be compressed only where it passes through muscles between the transverse processes. The first portion of the vertebral artery may be occluded readily by external pressure in the lower third of the neck, since it is surrounded by muscle.

The only arterial inflow to the brain which cannot be occluded by a cervical pressure cuff lies within the vertebral canal and passes up with the spinal cord, protected by bone. These vessels, the anterior spinal arteries, join the vertebral arteries just before the junction of the latter to form the basilar artery. These

15. Bingel, A., and Hampel, E.: Spättod nach Erhängen. Beitrag zur Klinik und Anatomie der Kreislaufstörungen im Gehirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:640, 1934. Footnote 8.

16. von Novak, E.: Ueber die intrakardiale Injektion, Deutsche Ztschr. f. Chir. **250**:310, 1938.

vessels are relatively minute in man. Since the chief source of supply for these vessels in the cervical region is the vertebral arteries, occlusion of the latter should also greatly reduce blood flow to the brain in the anterior spinal arteries. Furthermore, with stasis of blood in the brain resulting from occlusion of both arteries and veins, it seems unlikely that any quantity of blood could flow from the lower end of the brain stem through vessels filled with blood to supply oxygen to the sensitive cerebral cortex.

The venous return from the brain is chiefly through the internal jugular, the external jugular and the cervicalis profunda vein. These veins are surrounded by muscle and are readily occluded by a cervical pressure cuff.

The neurons in the brain are the cells of the body most sensitive to anoxia. There appear to be specific differences in sensitivity to anoxia in different centers of the brain. The great sensitivity to anoxia and hypoglycemia of cerebral neurons is due to their high metabolic rate, their failure to use stored glycogen for energy and their dependence on circulating dextrose, their low anaerobic glycolysis and their highly specialized character. The pronounced loss of function of the human brain resulting from brief periods of arrest of circulation appears to be due primarily to lack of oxygen rather than to lack of dextrose or accumulation of metabolites.

METHOD

The Kabat-Rossen-Anderson apparatus has been designed to induce temporary arrest of circulation in the human brain without affecting the respiratory tract. This is accomplished by means of a specially designed inflatable cervical pressure cuff, held down to the lower third of the neck. The pressure in the cuff rises to 600 mm. of mercury within one-eighth second. The subject himself, as well as the physician, controls the deflation of the cuff, which can be accomplished within a fraction of a second. The apparatus allows full observation of the sitting subject at all times for accurate recording. The reactions of the subject may readily be recorded by means of devices such as the electrocardiograph and the electroencephalograph. The sudden inflation of the cuff to a high pressure causes occlusion of the vessels to the brain before the next heart beat, so that engorgement of the cerebral vessels is prevented.

The pressure cuff has been improved in the course of this investigation, so that the earlier experiments on the schizophrenic patients and normal subjects are valuable chiefly for their qualitative observations.

The procedure has been applied repeatedly to the same subjects, with no injurious effects. Periods of acute arrest of cerebral circulation for as long as one hundred seconds appear to be well tolerated and are followed by rapid and uneventful recovery.

RESULTS

I. *Clinical Effects of Brief Periods of Acute Arrest of Cerebral Circulation in Normal Subjects.*—The characteristic reactions resulting from acute arrest of the circulation in the brain for five to ten seconds were fixation of the eyeballs, blurring of vision, constriction of the visual fields, loss of consciousness and anoxic convulsions. This response occurred with great rapidity and was uniform from subject to subject. Our procedure was to release the pressure in the cuff simultaneously with loss of consciousness by the subject. Recovery occurred quickly in every case, and the procedure was demonstrated to be free from danger. All subjects could stand, walk out of the room and go about their work within one or two minutes after the procedure, and no later effects were observed. In addition to the reactions already mentioned, some subjects showed turning up of the eyeballs and tingling or shooting pains in the extremities.

A. Eyes: Fixation of eyes: The earliest and most constant objective reaction to acute anoxia of the human brain was fixation of the eyes. This was tested by having the subject move his eyes rhythmically from side to side in the horizontal plane while they followed the moving finger of the examiner or a freely swinging

pendulum. In the usual subject, after five or six seconds of cerebral anoxia, the eyes fixed suddenly in the midline and the subject was incapable of moving the eyes, although he was still conscious (loss of consciousness occurred one-half to one second after fixation of the eyes). The subject stated afterward that he tried to follow the examiner's finger and could see it moving, but was unable to move his eyes. The great sensitivity to anoxia of the centers for voluntary motion of the eyes has been demonstrated by McFarland, Knehr and Berens [17] in studies on the effects of breathing gas mixtures low in oxygen on ocular movements associated with reading. It appears likely that this disturbance of function of extraocular muscles is dependent on derangement of cortical rather than of subcortical activity.

Turning up of the eyes: In some subjects, about one-half second after fixation of the eyes in the midline, the eyeballs suddenly turned upward, the reaction coinciding with loss of consciousness and immediately preceding the anoxic convulsion. These subjects were usually sensitive to cerebral anoxia and had a more severe convulsive seizure than usual.

Subjective ocular symptoms: Before loss of consciousness, many subjects experienced rapid narrowing of the field of vision, blurring of vision, with the field of vision becoming gray, and, finally, complete loss of vision. A number of subjects stated that they were unable to see but could still hear and were conscious. Occasionally subjects reported that they experienced positive or negative scotomas, such as light or dark streaks or spots or twinkling lights progressing inward from the periphery of the visual field. The last-mentioned phenomenon was observed particularly by a subject who suffered from migraine. The great sensitivity of the visual cortex to arrest of circulation has been observed in animal experiments,[18] as well as in studies on anoxia in human subjects.[19]

B. Anoxic Convulsions: These seizures were of a generalized tonic and clonic type; they were usually relatively mild and rarely continued more than six to eight seconds. No twitching of individual muscles was observed. There was no excessive salivation, and no subject fell from his chair, bit his tongue or suffered any injury. The convulsion was preceded by loss of consciousness, and the subject usually remained unconscious throughout the seizure and had no memory of it. Some subjects regained consciousness during the latter part of the seizure and reported that they felt themselves shaking but were unable to control it.

A point of considerable interest is the fact that the seizure occurred after release of pressure in the cuff, and rarely or never during the acute cerebral anoxia. Restoration of blood flow simultaneously with fixation of the eyes often aborted a seizure, while continuation of cerebral anoxia for one or two seconds after fixation of eyes resulted in a more severe and prolonged seizure. There was considerable variation in the severity and duration of the convulsions in different subjects and in the same subject at different times.

C. Paresthesias: These took the form of numbness, tingling and shooting pains, which were noted during the arrest of cerebral circulation and rapidly disappeared after restoration of blood flow. The paresthesias varied greatly in intensity, in some cases being relatively mild and in others consisting of severe shooting pains down the arm or leg, much like an electric shock, of sufficient intensity to force

17. McFarland, R. A.; Knehr, G. A., and Berens, C.: The Effects of Anoxemia on Ocular Movements While Reading, Am. J. Ophth. **20**:1204, 1937.

18. Weinberger and others.[5a] Kabat and Grenell.[7b]

19. Gellhorn, E.: Effect of Oxygen Lack, Variations in Carbon Dioxide Content of Inspired Air and Hyperpnea on Visual Intensity Discrimination, Am. J. Physiol. **115**:679, 1936.

the subject to release the pressure in the cuff. Only a little more than half the subjects reported paresthesias during arrest of blood flow in the brain, and paresthesias did not invariably occur in the same subject on repeated trials. The paresthesias were noted most frequently in the hands, arms, head and face, but were also observed in the lower extremities, back, shoulders, chest and abdomen and in a number of instances all over the body. The paresthesias appeared earlier than other reactions, several seconds before loss of consciousness. It is likely that these subjective sensory phenomena are the result of stimulation of the neurons of the postcentral gyrus, as an early phase of acute anoxia. Comparably brief periods of arrest of circulation in an extremity failed to produce paresthesias.

D. Loss of Consciousness: Usually within one second after fixation of the eyes the subject appeared dazed, his eyelids drooped, his head dropped down on his chest and he slumped in his chair. If the examiner counted the seconds aloud, the subject could recall only the count up to five or six, at which time he also appeared to lose consciousness. Consciousness was also tested by having the subject respond to the flashing of a green light by pressing a button which rang a buzzer. This response also disappeared slightly before the subject appeared to lose consciousness.

Although the subject was instructed to remove his finger from the jet as soon as he felt like it, and thereby release the pressure in the cuff, he failed to do so, despite loss of consciousness and an anoxic convulsion. The subject's hand thus appeared to "freeze" in that position and became incapable of voluntary or involuntary relaxation. It was therefore almost invariably necessary for the examiner to take the responsibility of releasing the pressure. Most subjects did not realize that they were holding on to the jet. Some stated that they did not feel like bothering to release the pressure. Others stated that they tried to remove the finger from the jet but were incapable of the movement.

A variety of mental symptoms were observed on the subject's returning to consciousness. The symptoms were brief and did not last more than fifteen to twenty seconds. The subject was dazed and appeared confused, usually having a foolish smile on his face. Some appeared temporarily excited and euphoric. Some insisted that they did not lose consciousness, although they had no memory of the convulsion and failed to respond to the flashing light. Others appeared frightened and tense for a few seconds and then suddenly relaxed, smiled and appeared normal. Some subjects did not respond to the flashing light for many seconds after restoration of circulation in the head but suddenly responded when ordered to do so by the examiner. They stated that they saw the light, knew they were supposed to respond by pressing the button, but did not care, did not want to bother and had no will or inclination to move. Schwab [20] has reported that the reaction to visual stimuli was absent or the reaction time was prolonged in petit mal attacks and that attacks were terminated more rapidly by auditory stimuli than by other kinds.

E. Electroencephalogram and Electrocardiogram: [21] The electroencephalographic changes corresponded to the records obtained from patients with orthostatic hypotension.[22] The sudden appearance of large slow waves was closely correlated with fixation of the eyes or loss of consciousness. No increase in

20. Schwab, R. S.: The Influence of Visual and Auditory Stimuli on the Electroencephalographic Tracing of Petit Mal, Am. J. Psychiat. **97**:1301, 1941.

21. Records were made under the supervision of Dr. E. J. Baldes.

22. Lennox, Gibbs and Gibbs.[12b] Forster and others.[13]

frequency was noted, an observation which supports the contention of Forster, Roseman and Gibbs [13] that the increased frequency of brain waves in cases of carotid sinus syncope of the central type indicates that cerebral anemia is not a major factor in this type of syncope.

Electrocardiographic changes were minimal, with slight sinus slowing in some subjects and no change in others.

II. *Effects of Prolonged Arrest of Cerebral Circulation in Patients with Mental Disease.*—Arrest of cerebral circulation for as long as one hundred seconds was carried out on 11 schizophrenic patients. These studies were made early with a technic which often failed to produce complete arrest of cerebral blood flow, so that the results were variable. However, qualitative changes resulting from these long periods of arrest of blood flow are of interest. In these tests the subject was supine.

Cerebral circulation has been arrested by means of cervical pressure for as long as one hundred seconds. All subjects regained consciousness within thirty to forty seconds after restoration of circulation in the brain and were able to walk from the room within two minutes after the procedure. Late effects have never been observed. During the arrest of circulation, loss of consciousness, convulsions, marked cyanosis, involuntary urination and defecation, bradycardia, dilatation of the pupils and changes in reflexes were recorded. Respiration was increased in rate and amplitude but continued throughout the procedure. After restoration of blood flow there was pronounced flushing of the face and consciousness soon returned, followed by interesting temporary changes in the behavior of the patient.

A. Pulse and Blood Pressure: In the first twenty to thirty seconds after arrest of blood flow in the brain there was no decided change in the pulse, a slight increase or decrease in rate being observed. As the arrest of circulation was continued, a notable slowing of the heart frequently occurred, sometimes to less than 50 per cent of the original rate. This bradycardia was readily prevented by administration of atropine sulfate and was apparently the result of direct stimulation of the cardioinhibitory center of the vagus nerve in the medulla by arrest of blood flow.[23] After administration of atropine arrest of cerebral circulation usually increased the heart rate.

The blood pressure was recorded immediately before arrest of cerebral circulation and immediately after restoration of the blood flow. Usually there was a moderate rise or fall of the systolic pressure, not exceeding 15 per cent, with less evident changes in the diastolic pressure.

B. Reflexes: Corneal reflex: In 150 trials the time of disappearance (survival time) of the corneal reflex was measured as accurately as possible. In the earlier studies, the corneal reflex either persisted throughout the procedure or disappeared as late as fifty to seventy-five seconds after inflation of the cuff. With improvement of technic and more complete occlusion of the cervical vessels, the survival time of the corneal reflex declined sharply and became more constant in repeated trials, so that the later trials may represent complete arrest of circulation in the brain.

In 1 patient the corneal reflex was observed to disappear six seconds after inflation of the cuff. In other trials with the same subject the survival time of the corneal reflex was recorded at eight and ten seconds. In another patient, on repeated trials, the survival times of the corneal reflex were seven, seven and one-

23. Kabat, H.: The Cardio-Accelerator Fibers in the Vagus Nerve of the Dog, Am. J. Physiol. **128**:246, 1940.

half, nine, nine, ten and ten seconds. In a third patient the corneal reflex was observed to disappear in ten seconds, and in a fourth subject, in eleven seconds. Since all of these studies were made before the apparatus was fully perfected, there is still some question concerning the completeness of arrest of blood flow in the brain in these trials. Therefore one may conclude that the center for the corneal reflex in man is extremely sensitive to arrest of cerebral circulation and that the survival time of the corneal reflex is undoubtedly less than ten seconds. This corresponds to the observation of Kabat, Dennis and Baker [6b] that the wink reflex in the dog, produced by touching the inner canthus of the eye, disappears within ten seconds after complete arrest of the circulation in the brain. The centers in the brain stem concerned with respiration, blood pressure and heart rate are evidently much more resistant to anoxia than is the reflex center for the corneal reflex. Furthermore, the areas of the cerebral cortex which inhibit the pathologic reflexes and maintain the abdominal reflexes also appear to show greater resistance to anoxia than the center for the corneal reflex.

The time for recovery of the corneal reflex was variable, depending on the duration of arrest of blood flow, as well as on the completeness of vascular occlusion. After one hundred seconds of cerebral anoxia, with a survival time of twenty seconds for the corneal reflex, several subjects had recovery times of twelve to twenty seconds. After thirty seconds of arrest of blood flow, with survival times less than ten seconds, the time for recovery of the corneal reflex varied from four to seven seconds.

In 1 patient the cochleopalpebral reflex (wink produced by a loud noise close to the ear) persisted seven seconds and, after twenty-five seconds of arrest of blood flow, was restored in nine seconds.

Abdominal reflex: This reflex is diminished or absent during prolonged arrest of the cerebral circulation. It was difficult to determine accurately the survival time of this reflex, but in several trials absence of the reflex was noted after ten, forty and fifty seconds. In 1 instance the abdominal reflex disappeared before the corneal reflex. Usually the abdominal reflex had disappeared before the appearance of pathologic reflexes. The abdominal reflex was still absent long after the restoration of the corneal reflex. After arrest of circulation for one hundred seconds, the abdominal reflex returned in two to four minutes after restoration of blood flow in the brain.

It is well known that frequently the earliest objective diagnostic sign of a tumor in the frontal lobe is the decrease or disappearance of the abdominal reflexes. The usual explanation is that the tumor first encroaches on the cerebral center for the abdominal reflexes because this area is more rostral in the brain than are the areas for the pathologic reflexes, such as the Babinski sign. This is pure hypothesis, since there is no conclusive evidence on the problem of localization of the center for the abdominal reflex in the cerebral cortex.[24] An alternative explanation suggests itself from the foregoing observations, namely, that the encroaching tumor, resulting in ischemia, first produces decrease or abolition of the abdominal reflex before the ischemia has affected the function of the cortical neurons concerned with pathologic reflexes, because of the greater sensitivity of the center for the abdominal reflex to decreased blood flow.

Pathologic reflexes: Various pathologic reflexes were observed to appear during prolonged arrest of the cerebral circulation and to disappear soon after restoration of the blood flow. The appearance of these reflexes was variable, but

24. Brock, S.: The Basis of Clinical Neurology, Baltimore, William Wood & Company, 1937, p. 63.

was usually preceded by decrease or disappearance of the abdominal reflexes. The Babinski, Hoffmann and Rossolimo signs, and occasionally the Gordon reflex, were tested for immediately before occlusion of the cervical vessels and repeatedly during and after arrest of the cerebral circulation. In 6 of 10 patients studied, the Rossolimo sign could be elicited during arrest of circulation to the brain, while the Babinski and Gordon reflexes could not be obtained and the Hoffmann reflex was elicited only occasionally. In 2 subjects the first appearance of the Rossolimo sign was recorded at fifty seconds after occlusion of the cervical vessels, and the reflex was noted to disappear within a few seconds after release of pressure in the cuff. In 8 patients, despite the disappearance of the abdominal reflexes and the appearance of other pathologic reflexes, tests for the Babinski and the Gordon sign gave uniformly negative results during the cerebral stasis. A Babinski sign was observed during arrest of cerebral circulation in 2 subjects, but in other trials on the same patients they could not be elicited throughout the procedure. In several patients a questionable Babinski sign was noted. The Hoffmann sign was not elicited in 6 patients and was obtained during arrest of circulation to the brain in 3 patients. In 4 subjects who presented a Rossolimo sign the Hoffmann reflex was consistently absent. In 2 patients, on the other hand, arrest of cerebral blood flow resulted in the appearance of a Hoffmann sign, while the Rossolimo reflex could not be obtained.

From these observations one may conclude that in man the cortical area concerned with the Babinski and Gordon reflexes, presumably area 4 of Brodmann, is more resistant to acute anoxia than is the cortical area for the Rossolimo and Hoffmann reflexes, presumably area 6 of Brodmann.[25] In most subjects area 6 for the foot (Rossolimo sign) was more sensitive to anoxia than area 6 for the hand (Hoffmann sign). In some subjects, however, area 6 for the hand was the more sensitive. The pathologic changes in area 6 were more severe than those observed in area 4 after relatively prolonged arrest (nineteen minutes) of the cerebral circulation in dogs.[26]

Involuntary urination and defecation: Seven of the 11 patients subjected to relatively prolonged arrest of the cerebral circulation showed reflex urination fairly consistently on repeated trials. Urination was noted fifteen to forty seconds after occlusion of the vessels supplying the brain. Two of these patients showed involuntary defecation thirty seconds after arrest of circulation to the brain.

C. Eyes: A number of observations were made on the eyes of patients during relatively prolonged cerebral anoxia. In 7 patients the eyegrounds were examined by means of the ophthalmoscope by Dr. Clyde Cabot. During the arrest of cerebral circulation there was observed moderate dilatation of the retinal veins, which became darker, the color corresponding to the degree of cyanosis present; the optic disks also became somewhat darker, while no change was noted in the retinal arteries. The eyegrounds were restored to normal within a few seconds after release of pressure in the cuff. Moderate dilatation of the pupils was observed twelve to twenty seconds after beginning of the arrest of cerebral circulation.

A characteristic feature of the response to acute arrest of the cerebral circulation in all patients was conjugate deviation of the eyes. This lasted only from a few to ten seconds and was frequently associated with the tonic phase of an epileptiform seizure. The conjugate deviation was consistently to the left and upward in 3 patients and consistently to the right and upward in 4 patients. In 1 sub-

25. Fulton, J. F., and Viets, H. R.: Upper Motor Neuron Lesions, J. A. M. A. **104**:357 (Feb. 2) 1935.

26. Kabat, H.: Unpublished observations. Kabat and Grenell.[7b]

ject the head was rotated temporarily to the side to which the eyes deviated. After this brief conjugate deviation, the eyes gradually returned to the midposition or rotated slowly to the opposite side. Usually the conjugate deviation of the eyes was observed soon after the disappearance of the corneal reflex. With relatively complete arrest of cerebral circulation conjugate deviation of the eyes was recorded in ten to twenty seconds.

D. Epileptiform Convulsions: The seizures which occurred during and after arrest of the cerebral circulation were atypical grand mal convulsions. They were brief and relatively mild and showed repeated alternating tonic and clonic phases. The clonic phase rarely lasted longer than ten seconds and was not always generalized. The patient was always unconscious during the seizure and had no memory of it. There was no increase in salivation. Consciousness was recovered rapidly, and no injury or later symptoms were ever noted.

Although the convulsions varied a good deal, one usually noted a tonic phase beginning about fifteen seconds after occlusion of the cervical arteries, followed at twenty to twenty-five seconds by a brief clonic phase. The first tonic phase of the seizure was frequently accompanied by conjugate deviation of the eyes. With relatively complete arrest of cerebral circulation for one hundred seconds, the mild seizure was over thirty to forty seconds after beginning of the arrest, and the patient was relaxed during the remainder of the period of cerebral anoxia; restoration of blood flow resulted in a brief tonic and clonic convulsion. In some patients alternating tonic and clonic phases continued throughout the period of circulatory arrest. One patient showed, after restoration of cerebral blood flow, apparent catatonia and a peculiar flexor rigidity of the left hand, which differed from carpal spasm.

E. Psychiatric Observations: No significant improvement in the psychiatric status of the schizophrenic patients was noted after repeated and relatively prolonged periods of arrest of cerebral circulation. In some subjects behavior was more nearly normal for several minutes after recovery of consciousness following prolonged cerebral anoxia. Two catatonic patients who had not spoken for a long time responded rationally to questions for several minutes after recovery. In several patients characteristic mannerisms disappeared during this period. The failure to demonstrate therapeutic effects from the procedure may perhaps be related to the fact that all the patients had suffered from schizophrenia for longer than five years, that some were greatly deteriorated and that all had failed to improve with insulin and metrazol therapy.

III. *Quantitative Studies on Normal Subjects.*—The exact times for fixation of the eyes and for loss and recovery of consciousness during brief periods of arrest of cerebral circulation were studied in normal volunteers. These determinations were carried out with the improved pressure cuff and apparatus, which produced complete arrest of circulation to the brain. The subject sat facing the examiner and was instructed to move the eyes rhythmically in the horizontal plane while they followed the moving finger of the examiner or a swinging pendulum. He was also instructed to respond to the flashing of a green light by pressing a button which sounded a buzzer. On some subjects electroencephalograms were obtained and the changes correlated with the clinical observations. Either the subject or the examiner could release the pressure cuff at any desired time. The usual procedure was for the examiner to restore cerebral blood flow simultaneously with loss of consciousness of the subject, so that the circulation to the brain was usually arrested for less than ten seconds.

The subjects were 126 apparently normal male volunteers, ranging in age from 17 to 31 years. Eighty-two of the men were inmates of the Minnesota State Reformatory, St. Cloud, Minn., and ranged in age from 17 to 25 years. The other subjects were at the Minnesota State Prison in Stillwater, Minn., and ranged in age from 21 to 31 years. Repeated tests were carried out on 85 of these subjects. Similar tests were also performed on the investigators and their associates.

The time from occlusion of the cervical vessels to fixation of the eyes in the midline could be measured objectively within one-half second by means of a stop-

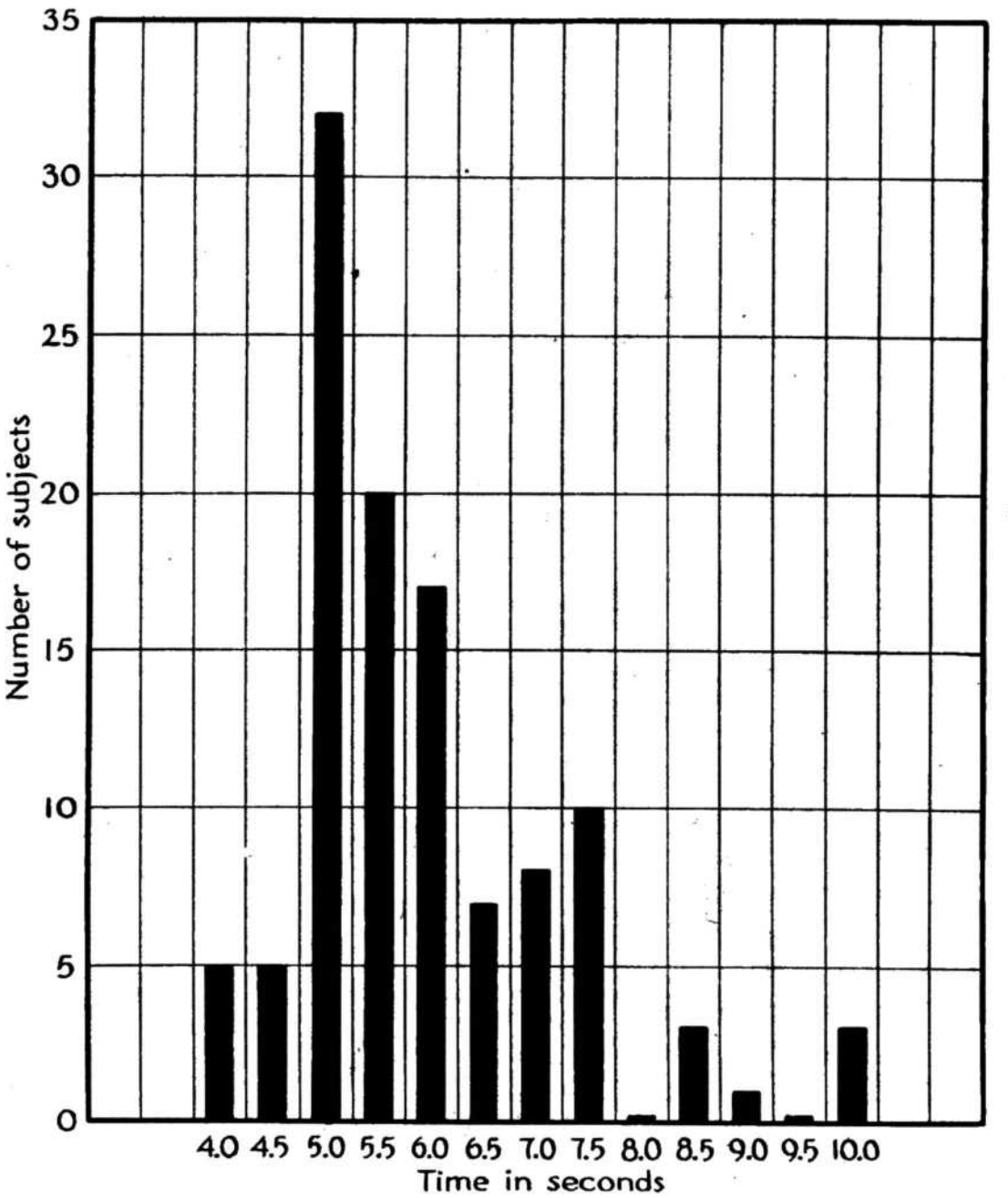

Fig. 1.—Distribution curve for time to fixation of the eyes during acute arrest of cerebral circulation in 111 normal young men.

watch. At this time the subject was still apparently conscious. A distribution curve for fixation time for different normal subjects is shown in figure 1. It is apparent from this graph that almost half the subjects tested showed fixation of the eyes five or five and a half seconds after initiation of cerebral anoxia. The relative constancy of fixation time on repeated tests on the same subject, illustrated in the table, suggests that cerebral blood flow was usually arrested completely by the KRA apparatus. Failure to respond to the light-buzzer test coincided in time with fixation of the eyes, while apparent loss of consciousness, characterized by sudden

slumping of the head and body, occurred about one second after fixation of the eyes. The delta wave usually appeared in the electroencephalogram about one second after fixation of the eyes.

The recovery time was measured as the time from fixation of the eyes to restoration of the response to the light-buzzer test. The time to fixation of the eyes, as a measure of resistance of the cerebral neurons to anoxia, might be expected to correlate with the time of recovery. Also, one would expect correlation of recovery of cerebral function and duration of arrest of circulation. Analysis of the data shows that there is no significant correlation between time of recovery and time of fixation or, within narrow limits, between time of recovery and duration of cerebral anoxia. The distribution curve for recovery times for 28 normal

Consistency of Time to Fixation of Eyes on Repeated Tests on Different Days*

Subject No.	First Test	Second Test	Third Test	Fourth Test	Subject No.	First Test	Second Test	Third Test	Fourth Test
1	5	5	5	7½	38	6	5	..	..
2	6	5	5½	5½	39	7	5½	..	..
3	5	7	5	9½	40	7	7	6½	..
4	10	12	..	..	41	5½	5½	5½	..
5	7	7½	6½	..	42	5½	5½	..	..
6	5	5	5½	..	43	5½	5	..	..
7	5	4½	..	..	44	4	5	5	5
8	4	4	4½	..	45	5	5	..	..
9	5	5	5½	..	46	6½	5	5	..
10	10	10	..	..	47	7	5½	5½	..
11	5	7½	9½	..	48	5	5	..	..
12	4½	5	5½	..	49	6	6½	5	..
13	6	6	7	..	50	5	5½	5	..
14	3	4½	4½	5	51	6	6½	6	..
15	5	5½	..	..	52	5½	5½	5	5
16	10	10½	..	..	53	6½	8½	7	..
17	7	7½	8	..	54	5	5½	5½	..
18	5	5	6	..	55	3	5	5	..
19	5	5	..	..	56	6½	7	7	..
20	4	4	..	..	57	7	6	6½	..
21	6	5½	5	7½	58	6	6½	6	..
22	5	8	..	..	59	7½	7½	7½	8
23	3	5½	5	..	60	5½	6	5½	..
24	6	5½	5½	..	61	4½	5½	5½	5½
25	6	5	..	..	62	6	6	5½	..
26	6	6	5	5½	63	7	6½	6	6
27	5	5	5	..	64	5	6½	5½	6
28	5	6	5	..	65	5	5½	5	5½
29	5½	5½	..	..	66	4½	5	..	..
30	4	5	5	6	67	7	5½	..	..
31	4½	5	..	..	68	8½	7½	..	..
32	4½	5	5	5½	69	7	7½	6	..
33	4½	5	5½	..	70	6½	6	..	..
34	7½	8	7	..	71	4½	5	..	..
35	4	4	..	..	72	6	7	..	..
36	4½	5	4¾	..	73	6	6	..	..
37	5	6	..	..	74	6	5½	..	..

* The fixation times are expressed in seconds.

subjects is shown in figure 2. The results of the first test were not used in determining the recovery time for these subjects because this test frequently showed prolongation of this period, due most likely to such factors as unfamiliarity with the test and apparatus and emotional reactions. The importance of such factors was emphasized by the observation that 1 subject had a prolonged recovery time on an occasion on which he became depressed and worried. On the other hand, his working until midnight and having the test early the next morning, before breakfast, had no influence on the recovery time. In tests for recovery time by this method, complex factors, chiefly psychologic, play a role as important as the sensitivity of the cerebral neurons to acute anoxia. The range of variations in recovery time on repeated tests on the same subject was much greater than that for the time to fixation of the eyes.

IV. *Effects of Preengorgement and Administration of Members of the Vitamin B Complex on the Response of Normal Subjects to Acute Arrest of Cerebral Circulation.*—The effects of preengorgement on the response to acute cerebral anoxia were investigated in 7 normal subjects, aged from 26 to 30 years. The preengorgement was produced by applying a pressure of 80 to 85 mm. of mercury in the cervical cuff for fifteen to eighteen seconds. This procedure obstructed the venous return without affecting the arterial inflow and presumably increased the concentration of carbon dioxide and other metabolites in the brain tissues. Within one second after release of the preengorgement pressure, the pressure in the cuff was raised suddenly to 600 mm. of mercury, with production of acute arrest of the cerebral circulation. Each subject was studied without preengorgement in three tests. Then, for the following three tests, preengorgement was produced,

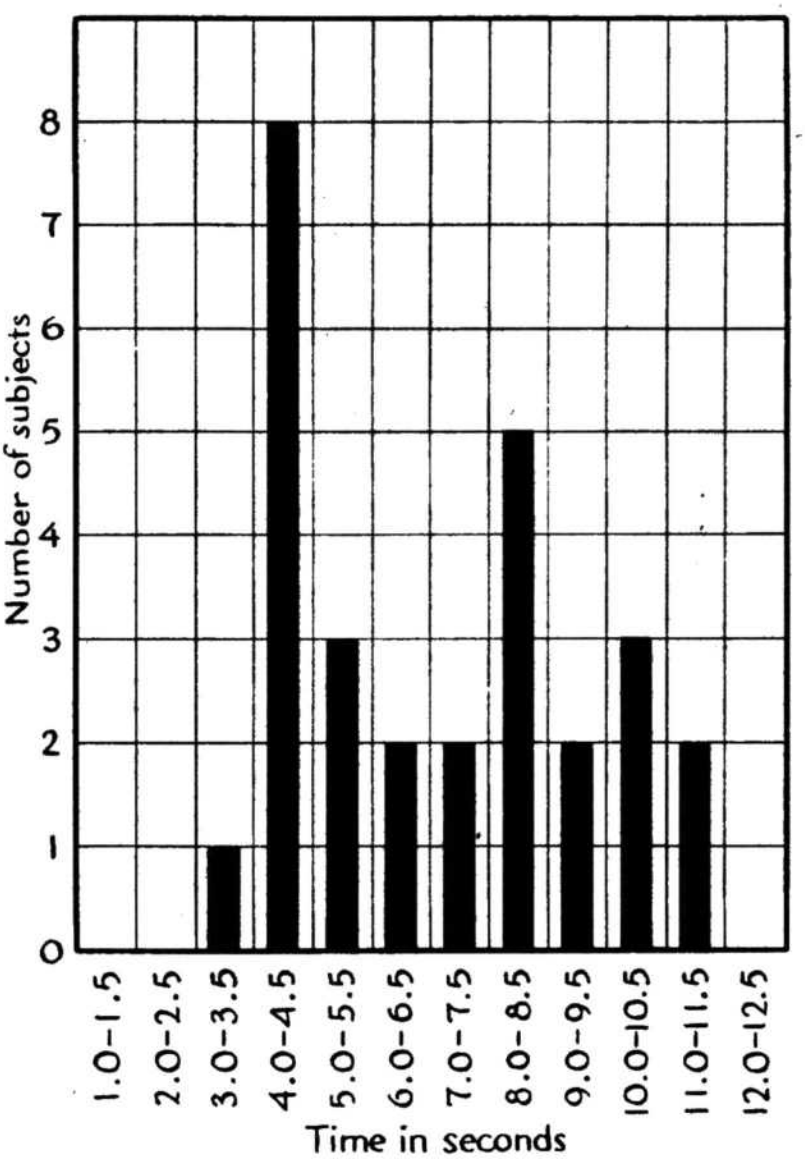

Fig. 2.—Distribution curve for time of recovery of the light-buzzer response following acute arrest of circulation to the brain in 28 normal young men. The graph shows average values on repeated tests (first test omitted).

as previously outlined. For the final test only acute cerebral anoxia was produced, without preengorgement. The duration of arrest of cerebral circulation was the same in all tests on the same person.

Preengorgement had no effect on the time to fixation of the eyes. The average fixation time without preengorgement was five and ninety-two hundredths seconds, and the average fixation time with preengorgement was five and nine-tenths seconds for the same subjects. This suggests that preengorgement fails to influence the sensitivity of cerebral neurons to anoxia. On the other hand, as illustrated in

figure 3, the average time for recovery of the light-buzzer response was reduced significantly by preengorgement. The final test on January 27, without preengorgement, showed a much longer recovery time than the three previous tests, with preengorgement. While there was a tendency for recovery to become more rapid with greater experience, this cannot explain the results with preengorgement illustrated in figure 3. Analysis of recovery times for individual subjects with and without preengorgement shows an even more striking acceleration of recovery with preengorgement. Perhaps the more rapid recovery may be related to improved circulation and utilization of oxygen in the brain after restoration of blood flow, as a result of increased concentration of carbon dioxide.

The influence of B complex vitamins in large doses on the time to fixation of the eyes and on time of recovery following occlusion of the cerebral blood supply was investigated in 9 subjects. Each subject was given daily oral doses of 200 mg. of nicotinic acid amide and 30 mg. of thiamine hydrochloride from January 13 to January 19. In addition, 3 of the subjects ingested 100 mg. of riboflavin

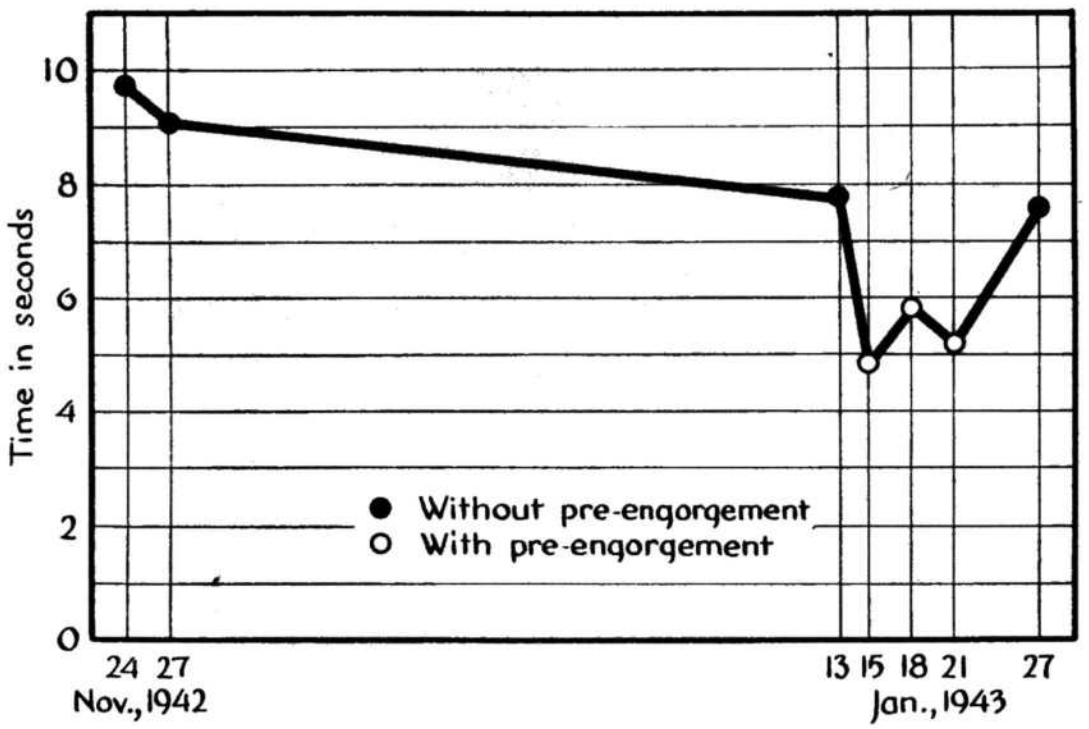

Fig. 3.—Effect of preengorgement on recovery time following acute arrest of cerebral circulation. The graph shows the average time of recovery for 7 normal young men on repeated tests.

from January 18 to January 26. The results on time to fixation of the eyes showed no significant change resulting from administration of the B vitamins: The average fixation time before vitamin B therapy was five and seventy-six hundredths seconds, and that during vitamin therapy was five and nine-tenths seconds. The effects on time of recovery of the light-buzzer response showed a moderate acceleration of recovery from cerebral anoxia with nicotinic acid amide and thiamine, either given alone or followed by riboflavin (fig. 4). In view of the small number of subjects and the complex nature of the test, these results should be considered only suggestive.

COMMENT

This is the first controlled investigation on the effects of acute arrest of the circulation to the human brain. Other methods, such as the study of patients with hypersensitive carotid sinus reflex [27] or the induction of orthostatic hypotension by posture or administration of nitrites,[13] cannot be controlled for comparison with

27. Footnote 11. Forster and others.[18]

the performance of normal subjects. Furthermore, the major factor in carotid sinus syncope is not usually arrest of circulation to the brain.[13]

One is impressed by the remarkable sensitivity of the function of the human brain to acute anoxia. The greatest number of subjects showed fixation of the eyes after cerebral anoxia for five to five and a half seconds and became unconscious after six to six and a half seconds. In studying syncope in patients with hypersensitive carotid sinus reflex, Weiss and Baker [11a] noted that after complete arrest of the heart consciousness was usually lost in eight seconds and regularly lost within twelve seconds. In some of their cases loss of consciousness occurred in five or six seconds. To explain such rapid loss of consciousness, they stated: "It is probable that in the latter cases, in addition to changes in systemic circulation, direct alterations in cerebral blood vessels also played a role." The data presented in the present report make such an assumption unnecessary. The somewhat longer maintenance of consciousness following cardiac asystole than with our procedure may be explained on the basis that arrest of the heart fails to arrest cerebral

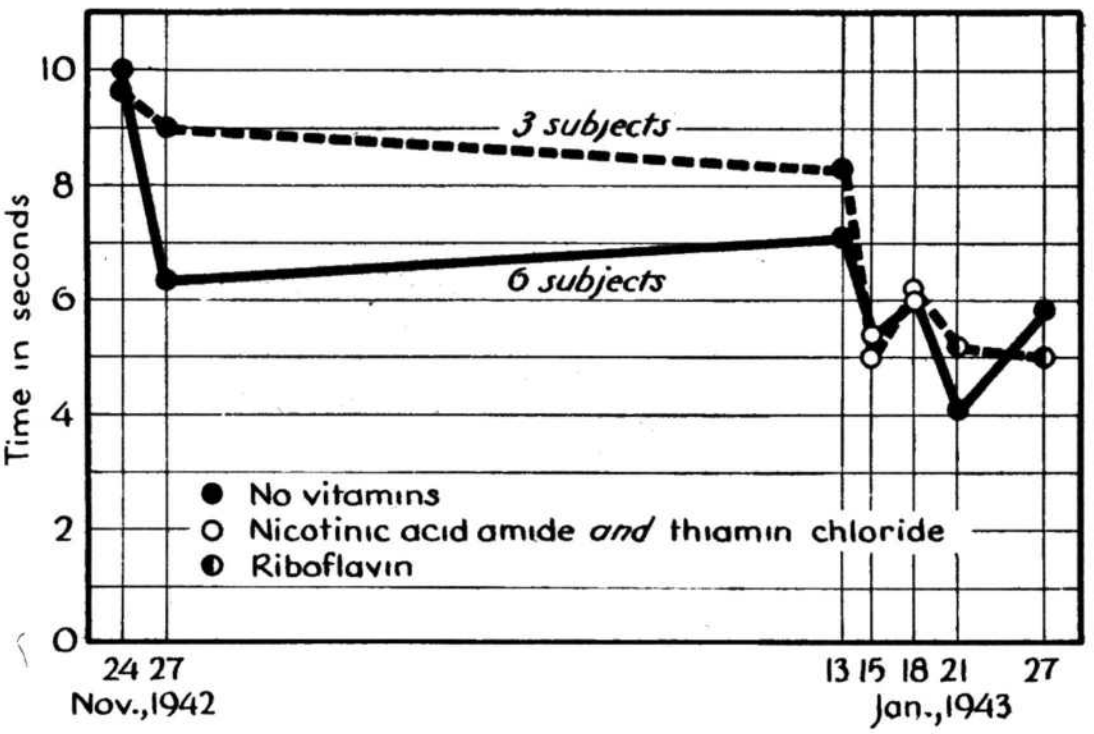

Fig. 4.—Effect of vitamin B therapy on recovery time following acute arrest of cerebral circulation. The solid line is the average recovery time for 6 normal young men on repeated tests; the broken line, the average recovery time for 3 normal young men on repeated tests.

circulation as rapidly as does occlusion of the arteries supplying blood to the brain. In cases of Stokes-Adams disease arrest of the heart was followed by loss of consciousness in ten seconds.[28] Such rapid loss of cerebral function also occurs in animals. For example, arrest of circulation to the brain in dogs resulted in disappearance of the corneal reflex within ten seconds.[6b] In cats, after occlusion of the chief arteries to the brain, action potentials disappeared from the cerebellar cortex in ten to twelve seconds and from the cerebral cortex in fourteen to fifteen seconds.[4] Older workers who reported much longer survival times obviously did not produce complete arrest of circulation to the brain.

While the sensitivity of the brain to anoxia, as determined by such measures as time to fixation of the eyes, appears to be fairly constant in the same person at different times (table), there is considerable variation from one subject to another

28. Penfield, W.: The Circulation of the Epileptic Brain, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:605, 1938.

(fig. 1). These individual differences in sensitivity to acute cerebral anoxia do not appear to be the result of incomplete arrest of the circulation to the brain. The constancy of response of the same person on repeated tests, as well as the demonstration that opacity of the ear does not increase during arrest of the circulation to the head by the KRA apparatus, indicates that circulation to the brain is arrested completely by this method.

The only factor besides circulation which would play a role in determining the sensitivity to cerebral anoxia is the metabolism of the neurons. Quantitative differences in utilization of oxygen by different brains could result in corresponding differences in the rapidity of loss of function following occlusion of the arterial supply to the brain. Differences in cerebral metabolism have usually been regarded as of no significance in studies on oxygen utilization of the human brain by arteriovenous oxygen measurements. Differences among individual subjects and differences associated with various diseases with respect to removal of oxygen from the blood by the brain have been ascribed entirely to differences in cerebral blood flow.[29] The assumption that cerebral metabolism is constant led Williams and Lennox [29a] to the dubious conclusion that 4 patients with high intracranial pressure who were in deep coma, from which they could not be roused, had "an increased rather than a decreased cerebral blood flow." The authors came to this conclusion by observing that the arteriovenous oxygen differences were somewhat lower than normal.

The range of variations in time to fixation of the eyes and to loss of consciousness in the studies presented in this paper, despite complete arrest of cerebral circulation, strongly suggests that the metabolism of the human brain varies from one person to another, even in healthy males ranging in age from 17 to 31 years. It is logical to expect individual variations in an organ as complex in structure and function as the brain, when it is well known that simpler systems show variations of considerable magnitude. Furthermore, similar individual variations have been noted in arteriovenous oxygen differences in the brain. Williams and Lennox [29a] reported a range of arteriovenous oxygen differences with various cerebral conditions as follows: high intracranial pressure, 4.33 to 9.83 volumes per cent; hypertension, 3.49 to 9.45 volumes per cent, and cerebral arteriosclerosis, 4.9 to 10.2 volumes per cent. Ferris [29b] reported in his patients a range of arteriovenous oxygen differences from 3.8 to 9.2 volumes per cent. Of greatest interest in this connection is the recent report of Gibbs and associates [30] on cerebral arteriovenous oxygen differences in 50 normal men from 18 to 29 years of age. They found an average arteriovenous oxygen difference of 6.7 volumes per cent, with a range from 4.5 to 8.5 volumes per cent. It is more than a coincidence that the distribution curve plotted from the data on arteriovenous oxygen differences reported by Gibbs and associates [30] corresponds so closely to the distribution curve for time to fixation of the eyes following arrest of circulation to the brain (compare figures 5 and 1).

Little interest has been shown in this wide range of individual variations in arteriovenous oxygen differences in the human brain. Usually it has been assumed that such variations represent quantitative differences in cerebral blood flow. However, it is questionable whether the cerebral blood flow varies so widely in normal young men under ordinary conditions. Indeed, students of cerebral blood

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29. (*a*) Williams, D., and Lennox, W. G.: The Cerebral Blood Flow in Arterial Hypertension, Arteriosclerosis and High Intracranial Pressure, Quart. J. Med. **8**:185, 1939. (*b*) Ferris, E. B.: The Effect of High Intracranial Venous Pressure upon the Cerebral Circulation and Its Relation to Cerebral Symptoms, J. Clin. Investigation **18**:19, 1939.

30. Gibbs, E. L.; Lennox, W. G.; Nims, L. F., and Gibbs, F. A.: Arterial and Cerebral Venous Blood: Arterio-Venous Differences in Man, J. Biol. Chem. **144**:325, 1942.

flow have placed great emphasis on its constancy. Thus, Lennox,[31] from studies of gases in the blood of the internal jugular vein, the cubital vein and the femoral vein, was impressed with the constancy of blood flow in the human brain. In 17 hospitalized patients, Ferris,[32] measuring the relative intracranial blood flow by a plethysmographic method, found a variation of from 118 to 171 cc. per minute. This is a range of variation considerably smaller than Gibbs and his associates observed for arteriovenous oxygen differences in normal healthy young men.

Under normal conditions the mean blood pressure is the most important factor in determination of the cerebral blood flow. "The systemic arterial pressure is more important in its effect on the total cerebral blood flow than any of the other factors (intracerebral or extracerebral)." [33] The mean blood pressure in men younger than 40 without signs of cardiovascular disease varied from 76 to 98 mm. of mercury.[34] Other workers, by direct determination of the mean blood pressure

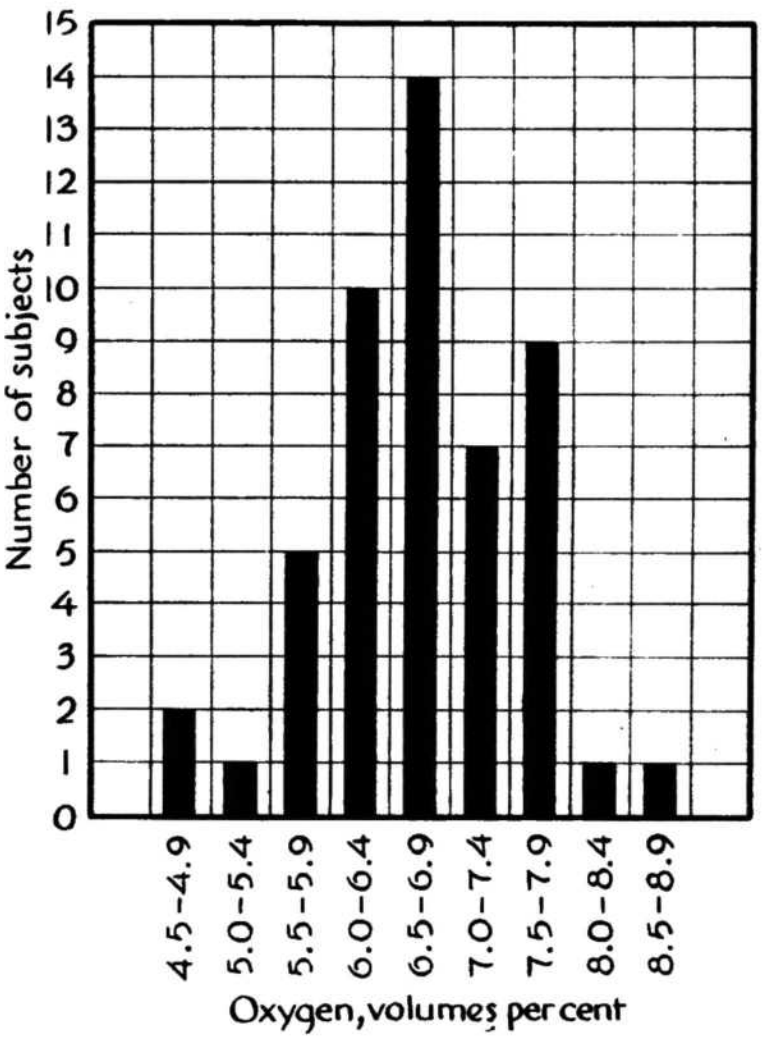

Fig. 5.—Distribution curve for cerebral arteriovenous oxygen differences for 50 normal young men, plotted from the table of Gibbs, Lennox, Nims and Gibbs (J. Biol. Chem. **144**:325, 1942).

by puncturing the femoral artery of subjects lying down, but not under basal conditions, have reported a range of variations from 70 to 95 mm. of mercury.[35]

31. Lennox, W. G.: Constancy of Cerebral Blood Flow, Arch. Neurol. & Psychiat. **36**:375 (Aug.) 1936.

32. Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, Arch. Neurol. & Psychiat. **46**:377 (Sept.) 1941.

33. Forbes, H. S.: Physiologic Regulation of the Cerebral Circulation, Arch. Neurol. & Psychiat. **43**:804 (April) 1940.

34. von Bonsdorff, B.: Zur Methodik der Blutdruckmessung, Acta med. Scandinav. **51**:7, 1932.

35. Laubry, C.; Beerens, J., and van Bogaert, A.: Tension moyenne intra-artérielle normale chez l'homme, Compt. rend. Soc. de biol. **113**:238, 1933.

Individual variation in cerebral blood flow may be expected to be small, since its chief determining factor, the mean arterial pressure, shows such a small range of variation. One may conclude, therefore, that the individual variation in cerebral arteriovenous oxygen differences in normal young men and the variation in sensitivity to cerebral anoxia noted by us may best be accounted for by variations in metabolism of the normal human brain.

From our data and the observations reported by other workers, it has been possible to calculate the average oxygen consumption of the brain in normal young men. From the data of Gibbs and associates [30] one may calculate that capillary blood in the brain would contain on the average 16.25 volumes per cent of oxygen. Assuming that the average weight of the brain is 1,360 Gm. and that 7 per cent of this weight is blood, from which oxygen can diffuse into the tissue,[36] one obtains a figure of 95 cc. of blood in the brain, trapped by the KRA apparatus. This quantity of blood contains 15.44 cc. of oxygen. Lennox, Gibbs and Gibbs.[12a] demonstrated that man becomes unconscious if the oxygen saturation in the internal jugular venous blood is 24 per cent or less. At a saturation of 24 per cent, the blood in the brain would contain 4.75 cc. of oxygen; when this is subtracted from 15.44, one obtains a remainder of 10.69 cc. of oxygen. This 10.69 cc. of oxygen must be used up in the period from initiation of arrest of circulation to the brain to the exact moment of loss of consciousness. The average time to loss of consciousness in our normal subjects was six and eight-tenths seconds. One thus arrives at an average volume for oxygen utilization of 1.56 cc. per second for the human brain, or a total of 4,140 cu. mm. of oxygen per gram per hour. According to Gerard,[36] the most reliable figure for total oxygen utilization in the animal brain is that of Schmidt,[37] who obtained a value of 4,500 cu. mm. per gram per hour for the dog brain. Gerard [36] recorded a value for oxygen utilization by the cat cortex of 4,000 to 5,000 cu. mm. per gram per hour. Our calculation of the amount of oxygen utilized by the human brain is probably a rough approximation to the average figure, but it suggests that the total cerebral metabolism in man does not differ greatly per unit weight of tissue from that of the dog or cat.

If the average human brain uses 1.56 cc. of oxygen per second, it requires 93.60 cc. of oxygen per minute. Since from each 100 cc. of blood passing through the brain 6.7 cc. of oxygen is removed,[30] the average blood flow through the brain which would satisfy this oxygen requirement is about 1,400 cc. per minute. This is close to 100 cc. per hundred grams of brain tissue per minute. Actual measurement of intracranial blood flow in man by Ferris [32] gave an average of 132 cc. per minute. He stated:

> Since the displacement rates for control subjects have ranged from about 125 to 150 cc. per minute, it is probable that the total intracranial blood flow of such subjects does not exceed 250 to 400 cc. per minute.

Such a small blood flow as Ferris postulated would fail by a wide margin to satisfy the oxygen requirement of the brain. The technic of Ferris, as well as the thermostromuhr of Gibbs, Gibbs and Lennox,[38] is of value in determining changes in blood flow produced by various agents, but gives little information concerning the exact quantitative measurement of the total blood flow. In dogs the average

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36. Gerard, R. W.: Brain Metabolism and Circulation, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:316, 1938.

37. Schmidt, C. F.: The Influence of Cerebral Blood Flow on Respiration: II. The Gaseous Metabolism of the Brain, Am. J. Physiol. **84**:223, 1928.

38. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow in Man as Influenced by Adrenalin, Caffein, Amyl Nitrite and Histamine, Am. Heart J. **10**:916, 1935.

blood flow recorded was 130 cc. per hundred grams of brain per minute.[39] In the rabbit Jensen[40] calculated a blood flow of 136 cc. and Winterstein[41] a blood flow of 60 cc. per hundred grams of brain per minute. In a recent investigation on the monkey, Dumke and Schmidt[42] observed a rate of cerebral blood flow of 86 cc. per hundred grams of brain per minute. It is probable that an average rate of cerebral blood flow of 100 cc. per hundred grams per minute is the correct value for various mammals, including man.

Since the cardiac output in man at rest is about 4 to 4.5 liters per minute, the blood flow through the brain is approximately one third of the total output of the left ventricle. This is remarkable since the brain represents only about 2 per cent of the body weight.

CONCLUSIONS

A new method, using the KRA apparatus, has been devised to produce complete arrest of the cerebral circulation in man.

Acute arrest of the cerebral circulation in normal young men results in fixation of the eyes, tingling, constriction of the visual fields, loss of consciousness and, immediately after restoration of blood flow, a brief, mild tonic and clonic seizure.

The average time from arrest of cerebral circulation to loss of consciousness in normal young men is six and eight-tenths seconds. This coincides with the sudden appearance of the delta wave in the electroencephalogram. One second before loss of consciousness one observes fixation of the eyes in the midline.

The time for recovery of the light-buzzer response depends on personality factors and does not correlate with sensitivity to acute anoxia. The time of recovery appears to be decreased by preengorgement and administration of large doses of the B vitamins.

Arrest of the circulation to the human brain for one hundred seconds may be followed by rapid recovery of consciousness and no objective evidence of injury. The corneal reflex may disappear in less than ten seconds. The abdominal reflex disappears, and the Rossolimo and Hoffmann reflexes often become positive during acute cerebral anoxia, while the Babinski reflex is not obtained.

Considerable individual variation has been noted in sensitivity of normal young men to acute arrest of circulation to the brain. This variation is apparently due to differences in cerebral metabolism in different persons. The resistance to acute anoxia is fairly constant for the same person at different times.

Calculations based on this investigation give figures for oxygen utilization of the human brain of 1.56 cc. per second, or 4,140 cu. mm. per gram per hour. This corresponds closely to figures for total brain metabolism reported for the dog and cat. To supply the brain with oxygen, the blood flow through that organ must average 1,400 cc. per minute, or about 100 cc. per hundred grams of brain weight per minute. At rest, the brain receives about one third of the output of the left ventricle, per minute, although it represents only 2 per cent of the body weight.

National Institute of Health, Bethesda, Md. (Dr. Kabat).

Anderson Institute for Biologic Research, Red Wing, Minn. (Mr. Anderson).

39. Gollwitzer-Meier, K., and Eckhardt, P.: Weitere Untersuchungen über den Nerveneinfluss auf die Hirndurchblutung, Arch. f. exper. Path. u. Pharmakol. **177**:501, 1935.

40. Jensen, P.: Ueber die Blutversorgung des Gehirn, Arch. f. d. ges. Physiol. **103**:171, 1904.

41. Winterstein, H.: Ueber den Blutkreislauf im Kaninchenhirn, Arch. f. d. ges. Physiol. **235**:377, 1935.

42. Dumke, P. R., and Schmidt, C. F.: Quantitative Measurements of Cerebral Flow in the Macaque Monkey, Am. J. Physiol. **138**:421, 1943.