The History of Anesthesiology

Reprint Series: Part Eight

NEUROANESTHESIA

Along with surgery in general, neurosurgery began to blossom around the turn of the century, as concepts of the treatment of disease changed, asepsis was adopted and anaesthesia was available to supply the requisite conditions. Still without professional anaesthesia, the pioneer neurosurgeons pondered over the usefulness of morphine for premedication, choice of chloroform or ether by inhalation, or cocaine via infiltration, and their effects on brain mass and bleeding. They worried, too, about the circulation and respiration and the consequences of operative positioning on morbidity and mortality.

Sir William Macewen of Glasgow performed the first successful craniotomy for tumor, in 1879, one year after he had been the first to employ an endotracheal tube during anaesthesia for resection of an oropharyngeal epithelioma. When Harvey Cushing began to specialize in brain surgery he quickly realized that better anaesthesia was needed than could be offered by the proverbial surgical intern. Accordingly in 1906 he enlisted the services of Dr. S. Griffith Davis in Baltimore, and recruited Dr. Walter S. Boothby in Boston around 1912. Thereafter the basics of cerebral physiology and pharmacology were defined by basic scientists and surgeons alike, as illustrated by the selected reproductions of articles provided in this packet.

Today, neuroanaesthesia is recognized as an essential discipline and full fieldged specialty of anesthesiology. As in the beginning, neuroanaesthetists in essence, are concerned about the effects of anaesthesia on brain mass and the quality of the circulation to it. In precise manner, they monitor these consequences as well as the sequelae of positioning of the patient for the specific operation underway.

Illustration from the Surgical Section (Chirurgie) of *Diderot's Encyclopaedia Recueil des planches sur les sciences et les arts*, 1772. (Courtesy of the Countway Library of Medicine, Boston, Massachusetts).

JOHNS HOPKINS HOSPITAL

BULLETIN

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between sea level and the highest point in the city is only that of a few hundred feet, and as I have already shown some of the worst infected districts are in sections of the city comparatively high, whereas in the neighborhood of the water front and Locust Point the disease is of unusually rare occurrence.

What may be the best practical methods of reducing the dangers from tuberculosis are problems of such enormity as to be entirely beyond the scope of a paper of this length, suffice it to say that it is only a question of time before our municipal authorities will be forced to adopt stringent regulations, such as have proven successful elsewhere in checking the spread of the disease. Maryland, unlike many of our States, has as yet done nothing, but the legislatures of New York and Pennsylvania have already passed laws requiring registration of all cases of tuberculosis at the offices of the health department, thus placing consumption upon the list of notifiable diseases. Dr. Herman Biggs, of the New York health department, at present estimates that he is enabled to have under surveillance 9/10 of all phthisical subjects. By forcing some and by teaching others to properly dispose of their expectorations, and by disinfecting the quarters of the patient after death, he believes that he has in the past six years reduced the mortality nearly 35%, which means the saving of 1500 lives annually. If to this society can be given the credit of stirring up in Baltimore such interest as may be necessary to insure the adoption of similar preventive measures, surely the idea which originated its foundation will have been a happy one.

N. B.—The numbers and boundaries of the city wards referred to in this paper are those which were in existence at the time of its first presentation.

CONCERNING A DEFINITE REGULATORY MECHANISM OF THE VASO-MOTOR CENTRE WHICH CONTROLS BLOOD PRESSURE DURING CEREBRAL COMPRESSION.¹

BY HARVEY CUSHING, M. D.

During the course of a long series of observations undertaken for Professor Kocher in the Physiological Institute of Bern in an attempt to elucidate certain questions of dispute regarding the circulatory phenomena which are consequent upon cerebral compression, it has been observed that there is a constant tendency on the part of the blood pressure to remain at a level above that of the pressure exerted upon the brain.

The fact that cerebral compression occasions a rise in blood pressure is universally known but it does not seem to have been recognized that the degree of this elevation occurs *pari passu* with the degree of compression (measured in millimetres of mercury) to which the medullary centres are subjected. It is ordinarily stated by the numerous experimentors who have dealt with problems of compression that fatal symptoms originate when the intracranial pressure approaches or reaches the height of the arterial tension. The fact that the arterial tension is a varying quantity which regulates itself so as to overcome the effects of the increased intracranial pressure seems never to have received attention.

In the greater number of my early observations the experimental compression has been made by means of quicksilver which was allowed to enter a thin rubber bag at the end of a metallic canula which was screwed into a trephine opening in the skull. By this method it was impossible to estimate with exactitude the degree of compression exerted against the medulla since the elasticity of the bag, the resistance of the dura in spite of its preliminary liberation from the skull, and the fact that the brain does not transmit the pressure from such a localized foreign body equally in all directions were always elements of uncertainty in the calculation. Nevertheless the method sufficed to call attention to the fact above mentioned, namely, that when the degree of compression was increased so as to exceed that of the blood pressure the latter would in turn almost invariably rise to a level exceeding that of the intracranial tension. In this way the blood pressure could be carried to indefinite heights, occasionally to 250 mm. of mercury or more, and be held there until the centres in the medulla became permanently fatigued.

The suggestion thus offered as to a definite regulatory mechanism which counteracts the compression anamia by elevation of blood pressure was further strengthened by direct observation, of the cerebral circulation through an accurately fitting glass window inserted in another trephine opening under which the dura had been opened. When the intracranial tension had been carried up to the point of blanching the convolutions and indeed of obliteration of the pial arteries themselves, it could be seen through this fenestra that this condition of anæmia was but a transient one, since in a few seconds the vessels would once more fill and the circulation become reestablished. On some occasions, to be explained later, the circulation could be seen to appear and disappear with rhythmic periodicity, the intracranial tension meanwhile remaining at the same level.

The opportunity of testing the truth of the hypothesis thus suggested has been offered in the *Laboratorio di Fisiologia* of Turin² where a simple but more graphic method of

¹Reprinted from the Archives Italiennes de Biologie for 1901.

⁹ I am deeply indebted to Professor Mosso in Turin and to Professor Kronecker in Bern for extending to me the privileges of their laboratories while carrying out these observations.

demonstrating this coincidence of blood pressure and degree of intracranial tension has been employed. In this Turin series of observations the animals employed have been invariably dogs. In Bern the same phenomena have been observed in other animals.

Method of Experimentation.—A preliminary injection of morphia has been given and the animals have been lightly anæsthetized with ether.

Blood pressure has been recorded from the femoral artery lest the ligation of one of the carotids should in any way disturb the intracranial circulation.

For direct observation of the circulatory condition of the brain a large trephine opening has been made in the median line in such a situation as to avoid the large emissary veins which pass between dura and diploæ not only from the great lateral cerebral veins anteriorly but posteriorly from the torcular itself. The dura is opened to one side of the longitudinal sinus exposing part of a convolution, its limiting sulci and the pial vessels. In the trephine opening an accurately fitting glass window is inserted through which the degree of distension or compression of the longitudinal sinus (unless the animal be very old), the condition of the capillary circulation in the exposed convolution and the vascularity of the pial vessels can be beautifully seen during the subsequent experiment.

The intracranial pressure has been produced and recorded as follows. Another, much smaller trephine opening is made over one part or another of the cerebrum, cerebellum or cord (in the latter case by trephining the lamina of one of the vertebræ). The underlying dura is carefully and freely opened. In the trephine hole an accurately fitting metal canula is screwed to which a firm rubber tube is attached communicating with a flask of physiological salt solution so arranged that it may be raised or lowered for the production of pressure to any desired level (cf. sketch). The rubber tube leads through a basin of hot water so that the fluid entering the cerebro-spinal space may be approximately at body temperature. The tube furthermore communicates with a mercury manometer which thus registers the degree of intracranial tension. In this way the cranial cavity is converted into a plethysmograph and the volume-pulse as well as the tension of the liquor can be graphically represented.

The blood pressure and intracranial tension may thus be recorded side by side on a kymographion, the manometers being so arranged that the zero pressures are taken from the same abscissa, (of sketch).

Respiration and time, the latter with a two second interval, are also recorded on the charts.

By the devices ordinarily made use of for the production of cerebral compression, especially by the introduction over the hemispheres of circumscribed bodies, solid or otherwise, no exact indication of the degree of pressure over the medulla is given since it is well known that pressure so applied is not transmitted equally throughout the three large cerebral chambers which are limited by tentorium and falx. In some animals indeed the brain may be so dislocated that the medulla may to a large extent be crowded through the foramen magnum and the vaso-motor centre thus partially escape from the compression effects to which the cerebrum is subjected. For this reason it was essential for our purposes to employ a method in which the intracranial tension over the fourth ventricle was to all intents and purposes equal to that which we were measuring in millimetres of mercury at the point of application of pressure. In no other way could an accurate comparison with the blood pressure be made.

It might be supposed and has heretofore been stated that the extraordinarily free communication between the cerebrospinal space and the cranial venous circulation would lead to a rapid overfilling of the right heart, should a continuous supply of artificial liquor under an abnormal pressure be afforded. As a matter of fact during life and when the blood pressure remains above that of the intracranial tension this escape of liquor is not exceedingly rapid. During a long experiment with the intracranial tension of this fluid varying from one to two hundred millimeteres of mercury and so held from ten to twenty minutes at a time, on an average only 80 to 100 cc. of the salt solution would be taken up by the circulation, certainly not enough to alter the reliability of the observations. On the other hand, after the death of the animal with a zero blood pressure the liquor enters the veins and thus the heart with much greater rapidity.

Care must be taken that the dura corresponding to the trephine opening for the canula be accurately excised and that the compression fluid be not allowed to enter from a high pressure with too great abruptness since under such conditions the dura may be flattened against the brain and the fluid collect as a foreign body between the membranes and skull instead of passing freely in all directions over the entire central nervous system. Under these latter circumstances and provided that the pressure from without is kept at a constant level the tension of the fluid in the cerebro-spinal space is the same throughout and the absorption which is in too small amounts to embarrass the cardiac action, may be disregarded. Thus, very slight, if any, differences can be observed in the regulatory mechanism to be described, whether the fluid be allowed to enter primarily, over cerebrum, cerebellum or cord.

The accompanying charts demonstrate more plainly than can any description the striking regulatory phenomena on the part of the blood pressure, as controlled by the vasomotor centre, which occurs during varying degrees of medullary compression.

Until the intracranial tension ("*Hirndruck*") exceeds that of the blood pressure, nothing more than the usual slight excitatory phenomena (cf. Chart I) are seen, indeed if the fluid enters easily without compromising the sensitive dura this primary quickening of pulse and respiration may be absent (cf. Chart III.)



PLATE XXXIII.

THE JOHNS HOPKINS HOSPITAL BULLETIN, SEPTEMBER, 1901.



PLATE XXXIV.

THE JOHNS HOPKINS HOSPITAL BULLETIN, SEPTEMBER, 1901.

When, however, the pressure is increased until it exceeds that of the blood pressure and especially if this high intracranial tension has been rapidly produced (as in Chart III) we may occasion momentarily the so-called major symptoms of compression with Kussmaul-Tenner spasms, evacuation of bladder and rectum, practical cessation of respiration and pronounced vagus effect upon the heart often with a complete "Stillstand" lasting from ten to twenty seconds. Then follows a release from this extreme vagus inhibition and the vasomotor centre begins to exert its striking influence.

In the more simple condition when the pressure has been increased more slowly (Chart I), these vagus symptoms are often avoided and the rise in blood pressure follows immediately upon the increase of "Hirndruck" to a level which temporarily exceeds it. Under these circumstances and when there has been no pronounced vagus effect (as in Chart III, where the sudden release from vagus inhibition has temporarily let the vaso-motor action run away with the blood pressure) it can be seen that the rise in blood pressure is merely sufficient to carry it above the level of the compression fluid, in other words an arterial pressure is called out which suffices once more to carry blood to the centres in the medulla. If, as in Chart III, an unnecessary elevation of blood pressure has primarily been occasioned it will fall and continue along a line representing a level slightly above that of the compression. Should the intracranial tension be again increased the same phenomena will be again repeated (cf. Chart I), and in this way the blood pressure may be forced to a level considerably over 200 mm. of mercury before the vaso-motor centre shows signs of giving way and fails to respond to the demands of an anæmic medulla. Within reasonable limits of compression, however, this compensatory action may be indefinitely prolonged.

On many occasions, as in Chart I, the blood pressure may be seen to rise and fall, above and below the line representing the degree compression, with a rhythmic periodicity of one form or another (Traube-Hering waves, etc.). This phenomenon is readily explained by observation through the glass window of the circulatory condition of the brain, a state of absolute anæmia accompanying those periods when the blood pressure is below the level of the compression line, an abundant circulation being present when it is above. As the average line of blood pressure is raised to a higher level by increasing again the degree of intracranial tension it carries with it this same rhythmic activity (cf. Chart I).

It is the object of this communication merely to state the existence of the regulatory function above described, and the writer makes no pretense at theorizing over the physiological laws which govern it. However, the following observations demonstrate that the process depends largely for its action upon the vaso-motor centre and the control which the latter exerts over the great splanchnic circulation.

1. If the vagi be divided and compression subsequently be made upon the brain, the blood pressure will be seen to correspond even more closely than before to the degree of intracranial tension (cf. Chart II) always remaining slightly higher than the pressure exerted against the medulla or else passing above and below it with wave-like rhythm. The vagus effect (as shown in Chart III) of course is absent under these circumstances.

2. If a coil of small intestine be exposed, during such a compression experiment as has been described, the splanchnic vessels can be seen to contract during the rise in blood pressure and to dilate once more as the latter falls at the end of the experiment.

3. Again if through a trephine opening in the atlas the spinal cord be divided with a blunt instrument so as to occasion the slightest possible bleeding, and then pressure be applied, the vagus effect alone will be forthcoming with no rise in blood pressure (cf. Chart IV), at least until the independent spinal centres shall have asserted their individual activity, when a slight rise may be occasioned.

4. If both vagi and cord be thus divided an increase in intracranial tension does not affect in the slightest degree the level of blood pressure (cf. Chart V.)

5. Similarly cocainization of the medulla by the introduction of the needle through the occipito-atlantal ligament, throws out the action of the bulbar centres. Under these circumstances, if artificial respiration be instituted the animal may live with a temporarily paralysed vaso-motor centre and an increase of intracranial tension does not affect the blood pressure until the cocaine effect begins to wear away.

As a result of these experiments a simple and definite law may be established, namely, that an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla. It is thus seen that there exists a regulatory mechanism on the part of the vaso-motor centre which, with great accuracy, enables the blood pressure to remain at a point just sufficient to prevent the persistence of an anæmic condition of the bulb, demonstrating that the rise is a conservative act and not one such as is consequent upon a mere reflex sensory irritation.

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EXPERIMENTAL ALTERATION OF BRAIN BULK

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In the early stages of an investigation of the factors underlying the swelling (edema) of the brain in acute infections or injuries, attention was directed to the possible relationship between the volume of the brain and the alteration in the pressure of the cerebro-spinal fluid, following intravenous injections of solutions of various concentrations (1). For in the study of cerebral edema, but little progress has in the past been made on account of the difficulty of experimental approach. This condition remains today one of the great problems in pathology of the central nervous system.

The marked changes in the pressure of the cerebro-spinal fluid, reported in the foregoing paper, were quickly found to have a definite relation to the resultant volume of the brain. Thus, following intravenous injections of strongly hypertonic solutions which markedly lowered the pressure of the cerebro-spinal fluid, definite shrinking of the brain occurred. And conversely the brain bulk was appreciably increased by the intravenous injection of hypotonic solutions, which raised the pressure of the cerebro-spinal fluid. Such changes in the size of the brain are rapidly and uniformly brought about, giving definite information as to one phase of the physiological regulation of the volume of this organ.

METHODS

Cats were used entirely in this work. Intravenous injections of the various solutions were given with a syringe or with a burette connected directly with a fore-leg vein. For the hypertonic solutions, 30 per cent sodium chloride or saturated sodium bicarbonate in distilled water were given, as previous work had demonstrated their efficacy in lowering the pressure of the cerebro-spinal fluid. Ringer's solution (NaCl, 0.9 per cent; KCl, 0.042 per cent; CaCl₂, 0.025 per cent) was injected intravenously to give data regarding the possible alteration in the circulation and in the volume of the brain brought about by the introduction of an increased volume of fluid, while distilled water was used as the hypotonic solution. Cats which had been given the customary intravenous injections of these solutions and then allowed to recover from the anesthetic, were usually a little slow for six hours but became normal and active within twelve hours. For the most part the observations were carried out on cats with unopened skulls, but in two series, subtemporal trephine openings were made, not only to relieve the intracranial tension but also to permit direct observation of the brain.

All animals used in these observations were anesthetized with ether. usually by intratracheal insufflation but in the earlier experiments by cone. The body temperature of the animals was maintained throughout. After the lapse of time necessary for the maximum action of the solution intravenously introduced, the animals were killed by ether. In the routine experiment, 10 per cent formalin was injected, immediately after death, through the aorta at a pressure of not more than 800 mm. o water. When the cranial vessels were well filled, the central nervous system was removed (the skull and vertebral canal being partially opened) and the whole immersed in 10 per cent for-In spite of all the care it was possible to exercise, it was soon malin. very evident that by this method of fixation, the form and size relations of the central nervous system prevailing prior to the death of the animal were not being accurately preserved. Brains markedly shrunken during life or at death of the animal approached almost normal proportions after such fixation, and brains markedly herniated at death often subsided perceptibly during preservation. The brains of other animals were fixed by direct immersion in formalin; the results of this method were similar in regard to alteration in volume. The addition of a suitable amount of sodium chloride to the formalin solution did not prevent these changes in brain bulk during preservation and was as unsatisfactory as other solutions.

Although the method of fixation used is inadequate, still it enables one to make general comparisons of the brains after various intravenous injections, even though it does not preserve the volume relations accurately. It is hoped there will be found a means of fixation which will preserve more exactly the form and size relations and at the same time make possible a study of the histology and cytology of these brains with reasonable confidence.

EXPERIMENTS WITH UNOPENED SKULL

The majority of these experiments were carried out on animals without opening of the skull. Some of this series, however, were used for determinations of the pressure of the cerebro-spinal fluid; in these the subarachnoid space was entered by a needle through the occipitoatlantoid ligament for connection with a manometer. In this limited manner the pressure relations within the cranium may be considered to have been altered; other animals of this series were carried through with intact cranial cavities.

Normal. Under this heading it is purposed to discuss the normal bulk of brains as found in cats killed without experimentation, and in those given Ringer's solution in such amounts as to control the volume of the other intravenous injections. The intravenous injections of Ringer's solution in these quantities did not alter the volume or appearance of the brain, so that, as far as our observations go, the brains of these animals are to be classed as normal.

When removed from the skull after routine fixation with formalin, the normal brain surrounded by unopened dura presents in the cat typical appearances. The dura over the convexities is only fairly well filled out and is under no appreciable tension, falling slightly between the adjacent gyri. On looking through the dura, a definite rounding of the convolutions and the fairly well-defined edges of the sulci are apparent. On transverse section of the normal brain (fig. 3), differentiation between gray and white matter is obvious. At the periphery of the section, the dura is seen to fall slightly between adjacent gyri. The surfaces of the gyri present smoothly-rounded curves, dipping into well-defined sulci of appreciable width. The median longitudinal fissure is clear cut and the adjacent gyri definitely separated. A line formed by the arachnoid membrane can be made out, bridging the larger sulci. Quite similar appearances are presented by the brains of animals receiving intravenous injections of Ringer's solution (fig. 4).

Examination of a large series of cats' brains fixed under similar conditions has shown that considerable individual variation exists. In brains of old animals, the gyri appear more rounded and the sulci deeper than in the younger cats. The dura in such older animals seems looser and denser, suggesting the various phenomena of old age exhibited by the brain in man. In very young cats and kittens, there seems to be a tendency toward swelling following formalin fixation. These individual variations, according to age, must be constantly borne in mind while interpreting the results of the experimental modification of the volume of the brain.

Hypotonic solutions. The intravenous injection of water, which has been found to produce a definite increase in the pressure of the cerebrospinal fluid, causes also a frank swelling of the substance of the brain. Amounts varying from 20 cc. to 100 cc. were injected intravenously: the degree of the reaction was apparently not dependent upon the absolute quantity of water injected, for the maximum effect observed occurred in a cat receiving only 20 cc. of water intravenously. Figure 1 gives the gross appearance of the formalinized brain of a cat which had been subjected to an intravenous injection of 35 cc. of distilled water, and sacrificed thirty-five minutes after completion of injection. The dura over the cerebral hemispheres is markedly tense as in all others similarly treated. The convolutions appear flattened when viewed through the dura and the sulci are traced with greater difficulty than in the normal. On passing the finger over the dura covering the upper surface of the brain, one receives an impression of marked tenseness of dura and brain, and recognizes the gvri and intervening sulci with difficulty.

On section, such brains (figs. 5 and 7) exhibit the same tenseness of dura previously noted. The normal differentiation between the gray and white matter has been diminished (figs. 3, 5 or 7). The convolutions appear definitely flattened, adjacent gyri being pushed together so as to make the identification of the intervening sulci difficult. This is particularly true of the smaller sulci. The surfaces of the gyri are no longer gently convex but acute angles in the curve are found where the surface dips into the sulci. The superior longitudinal fissure is narrow and the bounding gyri press tightly against the falx. The cut surface of the brain appears definitely turgid and gives the impression of having been subjected to increased tension.

An increase in the volume of the brain following the intravenous injection of water is therefore definite, marked and readily apparent.

Hypertonic solutions. The intravenous injection of strongly hypertonic solutions, which has been found to cause a profound lowering of the pressure of the cerebro-spinal fluid, has been observed to produce also a decrease in the bulk of the brain. This alteration in the volume of the brain has been brought about by intravenous injections of from 8 cc. to 20 cc. of 30 per cent sodium chloride or saturated sodium bicarbonate. As reported elsewhere under the subject of alterations in the cerebro-spinal fluid pressure, a marked individual variation in reaction

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to hypertonic solutions has been found to exist. The dose bringing about the maximal cerebral shrinkage varied, but in general the larger doses, approaching the limit of the animal's tolerance, seemed to cause the most marked effect. Some of the cats were given single injections of as much of the hypertonic solution as they seemed able to stand at one administration. Other animals were given a series of 5 cc. doses of 30 per cent sodium chloride at half-hour intervals, until a total of 20 cc. was injected. The animals, except when given the divided doses at half-hour intervals, were kept under ether anesthesia until sacrificed.

The time necessary for the maximum action of the fluid injected could not be determined accurately for the cats with unopened skulls. Assuming however, that the maximum lowering of the pressure of the cerebro-spinal fluid after such an injection coincides with the maximal diminution of brain-volume, it is probable that an interval of fifteen to twenty minutes suffices for the maximum change. Within certain limits, these observations substantiate this assumption, namely that the amount of fall in pressure of the cerebro-spinal fluid is an index of the extent to which the volume of the brain has been reduced.

The brain of a cat after the intravenous injection of a strongly hypertonic solution shows, on routine formalin fixation, a marked decrease in volume. As seen through the dura (fig. 2), which is very loosely applied, the brain seems comparatively small, occupying only a part of the intradural space. The gyri appear markedly rounded and the sulci wide and deep, so that individual convolutions appear throughout their extent. In the medulla oblongata and spinal cord there is also evidence of marked decrease in size. The dura here is very much more loosely applied than in the normal and the markings of the medulla oblongata and spinal cord seem sharp and accentuated. The general impression received from such an uncut brain is that it is quite small in comparison to the dural sac.

When cut transversely, the brain from a cat subjected to this experimental procedure presents an appearance quite different from the normal. The gray and white matter are far more sharply contrasted. Furthermore, the gray matter, particularly that of the thalamus and corpus striatum, appears dark with a brownish tinge, clearly outlining the nuclei from the adjacent white fibers. This phenomenon has been noted quite uniformly in this series. On such a section, the dura is very loosely applied (fig. 6), touching on the dorsal surface only the highest points of the gyri. Each individual gyrus stands out cleanly separated from adjacent gyri by widely opened sulci. The curve presented by the upper surface of each gyrus is of smaller radius than the normal, and may be followed deeply into each sulcus. The superior longitudinal fissure gapes widely and the falx seems to hang loosely within this space.

Similar shrunken brains have been obtained by the intravenous injection of saturated solutions of sodium bicarbonate. A section of such a brain is shown in figure 8, which presents in general the characteristic features noted above. The decrease in volume is, however. not so striking as in the brain reproduced in figure 6.

It was thought possible that the action of these hypertonic solutions might be enhanced by depriving such animals of all fluid for a sufficient length of time before experimentation to insure the exhaustion of a considerable quantity of the water available in the body. Two series of animals were thus prepared and injected with 30 per cent sodium chloride in 5 cc. doses at one-half hour intervals. While the cats receiving four 5 cc. doses showed the effects of the injection in a very marked way (gross clonus of whole body, mild mania, etc.), the brains failed to show any more, if as much shrinkage as is shown by the brains of animals not denied wc^{+-} . These observations indicate that deprivation of water for twenty-four hours in the cat is not sufficient to alter the fluid-volume of the body tissues available for reaction with hypertonic solutions.

In the unopened skull, then, a definite decrease in the bulk of the brain may be brought about by intravenous injection of strongly hypertonic solutions.

The supply of a foreign solution to subarachnoid space. At the end of a number of the experiments in which an intravenous injection of hypertonic sodium chloride was given, a mixture of sodium ferrocyanide and iron-ammonium citrate was allowed to flow into the subarachnoid space. This was done at a time when the pressure of the cerebrospinal fluid was about zero or falling rapidly. Two or three cubic centimeters were usually so introduced. At the end of the experiment the animal was injected through the aorta with 10 per cent formalin, to which 5 per cent hydrochloric acid had been added, and when the vessels were well filled the central nervous system was quickly removed and immersed in the acid formaldehyde. By this procedure, Prussian blue was precipitated at the points to which the solutions of sodium ferrocyanide and iron-ammonium citrate had penetrated prior to fixa-The Prussian blue in almost every case was found to have passed tion. from the subarachnoid space along the perivasculars into the substance

of the nervous system, reaching the interfibrous spaces in the white matter and the pericellular spaces in the gray. These observations may be interpreted as indicating that the hypertonic solution of sodium chloride, injected intravenously, had caused the dislocation of a considerable quantity of the cerebro-spinal fluid into the nervous system.

EXPERIMENTS WITH THE OPENED SKULL

The experiments dealing with the alteration of brain bulk by intravenous injection of solutions of varying concentrations were, in the earlier part of this investigation, carried out with the unopened cranial cavity, in which a fairly constant fluid volume was necessarily maintained. Even with such limitation to change in the volume of the brain, these solutions of various tonicities caused marked modification in its size. It was therefore thought desirable to carry out similar observations but with opening of the skull to permit expansion or contraction of the brain—changes impossible under the physical conditions imposed by the closed cranium. The rate of reaction to the intravenous injection and the appearance of the brain throughout the experiment could also, under these conditions, be determined by direct observation.

The opening of the skull was accomplished in the subtemporal region. In the etherized animal, through a midline incision, the temporal muscle on one side was freed from its origin, and a trephine opening of 2 cm. made in the skull beneath the muscle. The upper border of this opening came within 3 mm. of the mid-sagittal line of the skull. In another series bilateral subtemporal decompression openings were made. In every case the dura was freely opened by cruciate incisions. Injury to the underlying arachnoid and brain was carefully avoided.

Normal. Control experiments with single and bilateral decompressions were carried out. Following the opening of the skull, the animal was kept under ether until sacrificed at the expiration of about the same length of time as was consumed in the experiments where intravenous injections were given. In these control animals under such conditions the brain lay slightly convex beneath the trephine opening, pulsating freely, and did not change perceptibly in any way during the period of observation. The dural flaps were allowed to lie loosely on the exposed surface of the brain and throughout the experiment the edges of these flaps were separated from 1 to 2 mm. in the center of the trephine opening. At the end of these observations the animals were sacrificed with ether and the brains immediately preserved in 10 per cent formalin. On section, these brains appear quite normal with evidence of slight dislocation of brain substance toward the site of the trephine openings. Figure 13 shows a section of such a brain which was relieved by a single opening in the skull and dura; figure 16 represents the condition prevailing after a bilateral subtemporal decompression. It may be concluded, then, that under the conditions of experimentation the volume of the brain has been but little changed by the anesthesia and operative procedures employed.

Further control of the observations of brain bulk, following intravenous injection of solutions of various concentrations, is afforded by several experiments in which Ringer's solution was injected intravenously after single or bilateral openings had been made in the skull The injection of Ringer's solution was from a burette, and and dura. the rate of fluid-introduction was regulated to coincide with that used in the injection of similar amounts of hypotonic solutions. During and after the injection of Ringer's solution. in amounts up to 100 cc.. the brain lay slightly convex in the trephine openings, pulsating freely. and showed no evidence that it had been affected in volume by the intravenous injection. The appearance of the cortex viewed through the trephine opening was exactly that of the brain of an animal receiving no intravenous injection, but subjected to the other operative procedures. In figure 10 is shown the result (after fixation in formalin) of an experiment in which a single opening was made in the skull and 100 cc. of Ringer's solution injected intravenously. As pointed out previously, we have been unable with our present methods to preserve, by fixation in formaldehyde, the form and size relations prevailing in the brain at the end of experimentation. This figure shows a slightly more marked bulging of the brain in the trephine opening than was present at the end of the experiment. In spite of this slight swelling due to fixation it presents a fairly normal appearance, particularly when compared with more swollen or shrunken brains as shown in figures 9 and 11. In this and in all of our observations in which Ringer's solution was injected, the anesthesia, the operative procedures, the time consumed by the intravenous injection and the interval of time from the end of the injection to the sacrifice of the animal, were similar to those in the experiments in which solutions of various concentration were injected.

It may be concluded, then, that in etherized animals with the skull opened, the intravenous injection of Ringer's solution in amounts up to 100 cc. causes no appreciable change in the volume of the brain. The protocol of a typical experiment in which there was a bilateral opening of the skull and the intravenous injection of 100 cc. of Ringer's solution, is given below:

No. 1537. Adult male cat. Weight 2500 grams. Control intravenous Ringer.

- 9.46 a.m. Ether with intratracheal tube.
- 10.15 a.m. Double subtemporal decompression. Dura opened. Brain lies with normal convexity, pulsation and circulation good.
- 10.20 a.m. Cannula in vein of fore-leg connected with burette containing Ringer's solution.
- 10.25 a.m. Injection begun. Brain as before.
- 10.33 a.m. 25 cc. in. Brain as before.
- 10.38 a.m. 50 cc. in. Brain slightly more convex.
- 10.45 a.m. 90 cc. in. Brain as before.
- 10.50 a.m. 100 cc. in. Brain normally convex, shows no bulging. Pulsation free, circulation good. Injection stopped.
- 11.10 a.m. Brain lies normal as before. Pulsation free.
- 11.26 a.m. Brain lies normal as before. Ether to death. Immediately injected with 10 per cent formaldehyde until vessels well filled, then head cut off and immersed in same solution. Original relations fairly well preserved after fixation.

With the control afforded by these experiments in which the skull was opened and in which there was no intravenous injection, or else the introduction of Ringer's solution, an interpretation of the results of the intravenous injection of hypotonic and hypertonic solutions may be safely attempted.

Water. A number of observations on cats with single and bilateral openings of the skull have been made, during and following the intravenous injection of sterile distilled water which, as noted in a previous section of this paper, has been shown to bring about an increase in the volume of the brain in the unopened skull. The conditions prevailing in these experiments were similar to those maintained during the injection of Ringer's solution. In all these animals the brain, which lay normally convex in the trephine openings, began to protrude very soon after the intravenous injection of distilled water was started. This bulging increased throughout the period of injection and reached its maximum usually in from ten to twenty minutes after the completion of the introduction of water. Tense herniae of the brain through the trephine openings were thus produced. The tension was in all cases so great that cerebral pulsation ceased before the swelling reached its The pressure of the brain on the dura at the edges of the maximum. trephine openings was usually marked enough to stop the circulation in

the dural flaps. These triangular flaps were stretched, pulled and rolled back into the interval between the hernia and the cut edge of the trephine opening. Figure 9 shows the result of such an experiment and presents fairly well the appearance of the cerebral hernia before the sacrifice of the animal, although fixation in formaldehyde at death of the animal caused some subsidence of the hernia. When observed just before the death of the cat, usually thirty minutes after the completion of the injection of water, the brain protruded, in most of our experiments, at least 4 mm. beyond the outer table of the skull; in one animal which gave a very marked reaction, the height of the hernia at the end of the observation was 8 mm.

The protocol of an experiment in which there was a bilateral opening of the skull and the intravenous injection of 100 cc. of sterile distilled water, is given below:

No. 1536. Adult female cat. Weight 2,430 grams. Intravenous water

- 3.50 p.m. Ether with intratracheal tube.
- 4.00 p.m. Double subtemporal decompression.
- 4.15 p.m. Dura opened. Brain lies with normal convexity, pulsating freely. No trauma to brain or membranes.
- 4.18 p.m. Cannula in vein of fore-leg connected with burette containing sterile distilled water.
- 4.19 p.m. Injection begun. Brain bulges immediately after beginning of injection.
- 4.25 p.m. Brain bulges more.
- 4.31 p.m. 50 cc. in. Brain bulges markedly with pulsation; circulation good.
- 4.35 p.m. 75 cc. in. Brain bulges markedly: Pulsation slight, circulation good.
- 4.45 p.m. 100 cc. in. Injection stopped. Brain in tense hernia. Pulsation slight on left side. No pulsation on right side.
- 5.00 p.m. Brain markedly herniated. No pulsation on either side.
- 5.15 p.m. Brain in tense hernia on both sides--stops circulation in dural flaps.

5.16 p.m. Ether to death. Immediately injected through the heart with 10 per cent formalin and when vessels filled, head cut off and immersed in same solution. After immersion hernia remains about as before. Convolutions slightly more rounded and whole hernia slightly flatter.

On section, these brains present the appearance seen in figure 12 (after single decompression) and in figure 15 (after bilateral opening of the skull). A considerable dislocation of brain substance is apparent with some flattening of the gyri and narrowing of the sulci; but the general impression gained from an examination of these sections is different from that resulting from observation of sections, as shown in

figures 5 and 7, of brains obtained from animals subjected to the intravenous injection of water, but with unopened skulls. In the sections of the brains which were allowed to herniate, the impression of extreme tenseness and turgidity is not outstanding as is the case with the brains which were restrained by unopened dura and skull. The difference is undoubtedly to be explained by the different mechanical limitations to expansion present in the two types of experiment.

It is apparent from the foregoing that, under experimental conditions similar to those prevailing in the control observations on brains with opened skull (with or without the intravenous injection of Ringer's solution), the intravenous introduction of water causes a marked herniation of cerebral substance resulting from the increase in the volume of the brain. It is also worthy of note that the gross appearance of sections of such brains is different from that previously observed in sections of brains of animals receiving water intravenously but with unopened skulls.

Intravenous injections of a hypertonic solution (30 per cent Salt. sodium chloride), which produced a marked reduction in volume of the brain in animals with unopened skulls, have been given to a number of cats in which openings in the skull and dura were made on one or both The conditions prevailing in these experiments were similar to sides. those already described for the control observations. Following the intravenous injection of 30 per cent sodium chloride, the normal convexity of the brain in the trephine opening disappears soon after the injection is begun, so that the brain is seen to lie flat. As the intravenous injection of the salt is continued, the brain falls away from the skull until the surface presented becomes concave. The maximum shrinkage has been observed usually in from fifteen to thirty minutes after the completion of the injection, when the brain lies flaccid, 3 to 4 mm. below the inner table of the skull, with only very slight visible In figure 11 is shown the result of an experiment in which pulsation. a single opening was made in the skull, and $16\frac{1}{2}$ cc. of a solution of 30 per cent sodium chloride injected intravenously. The photograph reproduced in this figure was taken after the fixation of the head in 10 per cent formalin and does not show the marked shrinkage which was so striking at the end of the experiment. As has been emphasized, the methods of fixation employed do not preserve, with the accuracy desired, the relations existing during life; in spite of this difficulty it is readily apparent, from figure 11, that here the skull is only partially filled by this marked'y shrunken brain.

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The individual reaction and tolerance of cats to intravenous injections of a hypertonic solution of sodium chloride and the quantities most effective in producing a decrease in the volume of the brain, have been discussed in a preceding section of this paper. In these observations with the opened skull, doses approaching the limit of the animal's tolerance (16 to 20 cc.) have been administered; the same differences in individual reaction and tolerance, noted before, have been observed.

There is given below the protocol of a typical experiment in this series, in which there was a bilateral opening of the skull and dura and an intravenous injection of 20 cc. of a hypertonic solution of sodium chloride:

No. 1535. Adult female cat. Weight 2250 grams. Intravenous NaCl.

- 9.35 a.m. Ether with intratracheal tube.
- 10.10 a.m. Double subtemporal decompression.
- 10.15 a.m. Dura opened. Brain lies with normal convexity, pulsating freely. No injury to brain or membranes.
- 10.20 a.m. Cannula put in vein of fore-leg and connected with burette containing 30 per cent NaCl (Squibb)
- 10.23 a.m. Injection begun. Convexity of brain normal:
- 10.30 a.m. Brain as before. No hernia.
- 10.35 a.m. 11 cc. in. Both sides of brain receding-lie flat.
- 10.40 a.m. 14 cc. in. Brain fallen more-lies concave.
- 10.45 a.m. 16 cc. in. Brain fallen more.
- 10.50 a.m. 19 cc. in. Brain fallen still more.
- 10.54 a.m. 20 cc. in. Injection stopped. Brain markedly fallen. Circulation good, pulsation slight.
- 11.05 a.m. Brain markedly shrunk. Pulsation slight. Animal in good shape.
- 11.25 a.m. Brain far receded, pulsation slight. Brain lies 3 to 4 mm. away from the inner table of the skull.
- 11.26 a.m. Ether to death. Immediately injected through the heart with 10 per cent formaldehyde plus 1.5 per cent NaCl with cat lying on belly. Head cut off when vessels well filled and immersed in same solution. Within a few minutes after immersion brain rose in skull almost level with trephine opening.

After fixation in formalin and section, these brains, taken from animals with opened skulls and with intravenous injection of 30 per cent sodium chloride, are characterized by the condition shown in figure 14 (single skull opening) and figure 17 (bilateral subtemporal decompression). That there has been a decided decrease in the volume of the brain in both these cases is quite evident. Figures 12, 13 and 14 show sections of a series of brains taken from animals in which there was a single subtemporal decompression. In one animal (fig. 12) water was

injected intravenously; in another (fig. 14) 30 per cent sodium chloride, while in the third, (fig. 13) no injection was given. Figures 15, 16 and 17 show sections of brains from another series of animals in which bilateral openings were made in the skull and dura. Intravenous water was given in one animal (fig. 15), intravenous 30 per cent sodium chloride in another (fig. 17), but in the control (fig. 16) nothing was injected. A glance at these figures is quite sufficient to show that in the animal receiving the intravenous injection of a solution of hypertonic sodium chloride in both series, the brain has been markedly decreased in volume. A close examination of figures 14 and 17, and a comparison of these figures with figures 6 and 8, which resulted from experiments in which hypertonic solutions were injected intravenously but with the skull unopened, is extremely interesting in that, while there is evident shrinkage in both types of experiment, the way in which the brain was affected is different in the two. From figures 14 and 17 (opened skull) one gets an impression of marked compactness of the brain as a whole; this phenomenon is not so apparent in figures 6 and 8 (unopened skull). The well rounded gyri and the clearly apparent sulci, previously described as characteristic (following intravenous injections of hypertonic solutions) of brains arising from experiments in which the skull was unopened, are not to be found in brains after similar experimental procedures but with the skull opened. It is evident, then, that with the operation of the same factor which tends to produce a decrease in the volume of the brain, the form of the end result in the two cases is altered by the mechanical conditions imposed by the opened or unopened skull. It is thus apparent that when the brain is allowed by an opened skull to shrink and contract freely, the appearance of a greater decrease in total volume is obtained than in experiments where the force producing the reduction in volume must, as it were, pull against a partial vacuum furnished by the intact skull.

These observations make it clear that in brains unrestrained by the physical limitation of the closed cranium there is a marked decrease in volume after intravenous injection of hypertonic solutions of sodium chloride; but the resulting picture is different from that described for brains shrunken, after similar injections, within an intact skull.

In the course of the above experiments the failure of the brain of a very old cat to show marked swelling after the intravenous injection of water led to several observations on decidedly old animals. Two very old cats, following double temporal decompression, were given intravenous injections of 100 cc. of water. The brain of neither cat her-

niated markedly from increase in bulk. Another old cat, after double temporal decompression, was given an intravenous injection of 20 cc. of 30 per cent sodium chloride. The brain shrank away from the skull to a considerable extent, although not so far as is usually the case in younger individuals. It has been frequently noted that when exposed to view by operative procedure, the brains of these old cats look different from those of vounger individuals. While they pulsate freely in the decompression openings, they lie flat and do not show so much convexity as is characteristic of the brains of younger individuals. The sulci of these brains of old cats seem wider and the gvri more rounded than those characteristic of younger cats. That the brains of these old animals react less readily to intravenous injections by changes in bulk than the brains of younger individuals seems certain from these observations: that increase in volume should be more difficult than decrease seems reasonable, in view of certain mechanical and other conditions existing within the cranium in old individuals.

Two very young cats weighing 1,300 and 1,500 grams, were selected as typical young adults, in which changes in brain bulk should be outspoken. Following double subtemporal decompression, one received an intravenous injection of 100 cc. of water, the other 16 cc. of 30 per cent NaCl. Both showed very well marked reactions, developing relatively as great swelling or shrinkage as has been seen in any animal.

HISTOLOGICAL EXAMINATION

The pronounced swelling, which occurs in the cat's brain after the intravenous injection of water, and the marked shrinkage which follows the intravenous injection of strongly hypertonic solutions, has led to the desire to correlate, if possible, these gross alterations with histological changes in the cerebral substance.

Mention has already been made in this paper of the fact that fixation with formaldehyde does not preserve accurately the gross form and size relations of the brain as seen prior to death of the animal, so that the preliminary observations here recorded may represent only very roughly the histological picture accompanying the various modifications of brain bulk. That there are marked histological changes is readily seen but their exact interpretation, particularly in regard to the representation of conditions prevailing prior to fixation, is a matter requiring further study. It is hoped that when a method of fixation is devised which will preserve the form and size relations accurately, more intelligent histological and cytological observations may be made. The present findings are reported tentatively, pending an attempt to control the artifacts probably introduced by the technical methods employed.

The material available for this study was that resulting from the experiments described in the preceding parts of this paper. This material was preserved in formaldehyde, which was in most cases injected through the aorta immediately after the death of the animal. One series of brains fixed by Formaline-Zenker's fluid was used in an attempt to control the material preserved in formaldehyde. Sections were cut in paraffin, 10 μ thick; stained with haematoxylin and eosin, toluidine blue and fuchsin S, and with Mallory's and Van Gieson's connective tissue stains. All sections were made from blocks of cortex including the sulcus lateralis and parts of the two adjacent gyri, taken from the dorsal surface of the brain in the same transverse plane as the optic chiasma. In the animals where the skull was opened during the experiment, this block of cortex was found to be in the upper part of the trephine opening. Examination of sections of cortex taken from animals used in this study quickly showed that, when judged by the histological changes which accompany or follow gross shrinkage or swelling, these animals may be divided into two groups; those in which the skull and dura were opened during the experiment and those in which the cerebral cavity remained intact. The histological changes seen in sections of non-decompressed brains following various intravenous injections are quite marked and constant in the material studied, but sections from decompressed brains fail to exhibit the same marked differences from the control. It is quite evident, then, that following decompression the brain may adjust its volume; it may herniate, being only partially restricted by the dura, or collapse freely. This comparative freedom to contract or expand probably explains the finding of similar histological pictures in the normal decompressed controls, and in the decompressed brains following intravenous injection of water or All the specimens tended to approach the normal when the salts. brains were allowed to contract or expand with freedom, but when the alterations in cerebral volume were limited by the closed cranium, the factors responsible for the macroscopic changes in brain bulk produced also marked microscopic changes. Although these histological changes as observed have doubtless been altered by the technical methods employed in the preservation of these brains, their constancy is ample evidence that they are indicative of certain fundamental changes in the brain substance, even though they may represent very

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inaccurately the actual conditions prevailing prior to death. The technical procedures employed have been practically uniform for all brains, so that the artifacts produced may be considered as constant.

Skull unopened

Normal. Control sections were made from blocks of cortex taken from animals receiving no intravenous injection and from animals in which Ringer's solution was introduced intravenously. While it is apparent that there are artifacts in these sections, due probably to the method of fixation, they furnish a reasonable control for sections of brains taken from animals receiving intravenous injections of various concentrations. An examination of sections made from brains of animals in which Ringer's solution was introduced intravenously and a comparison of these sections with normal controls shows no fundamental differences in the two, so far as our observations go. These sections, then, furnish a reasonable standard with which the sections from animals subjected to other experimental procedures may be compared.

Water. The general appearance of sections of the cortex made from non-decompressed brains following the intravenous injection of water. is that of a swollen tissue. The sulci are quite narrow and the gyri tend to be flat. The smaller vessels seem, if different from normal, contracted within normal or slightly expanded perivascular spaces. The intercellular material of the gray matter seems inflated, the spaces found among the interlacing cell processes appearing larger than in control sections. Many of the large dendrites which rise perpendicular to the free surface of the gyrus are apparently larger than in the normal. Under higher magnifications the nuclei of nerve cells seem compact, the whole nucleus being perhaps slightly contracted. About the cells in most of the water brains examined, there is an evidently enlarged pericellular space, the general impression being that the cell itself is contracted away from the surrounding tissue. The occurrence of enlarged pericellular spaces in the gray matter of the cortex, following the intravenous injection of water, is most striking and constant. Pericellular spaces are apparent in sections of normal cortex, particularly about the larger cells, but following the introduction of water intravenously these spaces, even about the smaller cells, are evidently considerably enlarged. In this material the enlarged pericellular spaces and other histological evidences of change may be interpreted as due

to conditions within the brain, different from those existing normally, and produced by the intravenous injection of a hypotonic solution.

Salt. Sections of the cortex taken from brains following intravenous injection of 30 per cent sodium chloride, under low magnification, show in general an appearance of tissue contraction, the sulci being wide and the substance of the brain condensed. In practically all of the salt brains examined, the cortical capillaries seem distended. This distension may be explained partially, perhaps, by the arterial injection with formaldehyde (a procedure carried out with the normal and water brains) but it is a constant finding in the salt brains and may be taken as an indication of some constant factor in the fluid concentration within the nervous tissue. In most of the salt brains the perivascular spaces are apparent but not enlarged. The intercellular felt-work in the gray matter seems compacted and denser than in normal sections. The outstanding feature of the histological picture presented by these sections of salt brains concerns the occurrence of a marked clear space about the nuclei of many cells. These clear spaces vary in size from a slight space about a well-rounded nucleus to a wide space around a markedly crenated nucleus. These spaces increase in size in the gray matter from the medullary core out to the surface layers of each gyrus. The nuclei appear condensed, the chromatin being aggregated. The Nissl substance in the cytoplasm is at the periphery of the cell, the perinuclear spaces being between the nuclear membrane and a marginal ring of Nissl substance. In sections stained with toluidine blue and fuchsin S, these spaces are seen to be partially filled with a fluidcoagulum which stains with fuchsin. This coagulum in most cases has shrunk away from the nucleus toward and against the ring of Nissl substance. No pericellular spaces are usually apparent about the cells showing such perinuclear spaces. The pericellular spaces may be observed occasionally however in the deeper layers of the gray matter about the larger cells. As noted above, the perinuclear spaces are more marked and the nuclei more crenated in cells of the surface layers of the cortex. It seems evident, then, after a comparison of these sections with normal control sections, that in these brains the intracellular perinuclear spaces and other histological evidences of change in the brain substance may be attributed to changes brought about by the intravenous injection of a hypertonic solution.

Skull opened

Examination of sections of brains following intravenous injections of solutions of various concentration in animals with opened skulls reveals a histological picture quite similar in all. There are, of course, minor differences in the sections examined, but such differences do not seem to be due to any changes brought about by the intravenous injection. The decompression has evidently allowed each brain to expand or contract freely and to adjust its fluid distribution so that no essential histological differences are noticeable, all retaining very nearly a normal appearance. That there may be in these brains fundamental histological and cytological differences not revealed by the methods employed, is probable, but further work is necessary to establish such differences. With the methods employed it is certain that the decompressed brains do not show the histological characteristics which are so evident in the non-decompressed brains.

An exact interpretation of the above observations on the histological changes in the cortex of the brain following intravenous injections of hypotonic and hypertonic solutions can not now with reason be at-That there are histological changes in brains unrelieved by tempted. decompression is certain, but these changes need more accurate study and control before any sane effort can be made to explain them accu-The changes described have no doubt been influenced by the rately. technical methods employed; these methods may have, in addition, masked or destroyed other histological evidences of changes produced by the intravenous injections. Until one finds a method of fixation which will preserve the form and size relations of the brain accurately and at the same time will make possible accurate histological study, the above observations may be accepted tentatively as an indication that changes in the brain substance, recognizable histologically, do occur following intravenous injections of solutions of various concentrations.

DISCUSSION OF RESULTS

The experimental alteration of the volume of the brain by intravenous injections of hypotonic and hypertonic solutions has not, so far as we have been able to find, been previously recorded in the literature. The ease and rapidity of these changes in brain volume are of considerable interest in view of the old idea of the incompressible character of the brain and its relation to the conception of a constant vascular volume within the cranial cavity. The hypothesis that the volume of the blood circulating within the cranium must at all times be constant was first brought forward by Alexander Monro, the younger (2) in 1783. At this time he wrote that

as the substance of the brain, like that of other solids of our body, is nearly incompressible, the quantity of blood within the head must be the same at all times, whether in health or disease, in life or after death, those cases only excepted in which water or other matter is effused or secreted from the blood-vessels; for in these cases, a quantity of blood equal in bulk to the effused matter, will be pressed out of the cranium.

This viewpoint advanced by Monro was accepted and elaborated by Kellie (3) in 1824, who based his ideas upon observations on men frozen to death and upon experiments on animals. His conclusions were that a state of bloodlessness did not exist in the brains of animals killed by bleeding, that the quantity of blood in the cerebral vessels was not affected by posture or gravitation, that congestion of these vessels was not found in those conditions in which it might be well expected (hanging, etc.) and that compensatory readjustments between the different sets of cerebral vessels always maintained a constant vascular volume. Subsequently Kellie wrote

that in the ordinary state of these parts we can not lessen, to any extent, the quantity of blood within the cranium, by arteriotomy or venesection; whereas if the skull of an animal be trephined then hemorrhage will leave very little blood in the brain.

Within the next two decades following the publication of the results of Kellie's experiments, many clinical observations were reported in substantiation of this conception—that the vascular content of the brain was at all times practically constant. This Monro-Kellie doctrine received wide publicity through its acceptance by Abercrombie (4). This eminent surgeon, in discussing apoplexy, thus summed up his views on the subject (p. 300):

In this investigation it is unnecessary to introduce the question, whether the brain is compressible, because we may safely assert that it is not compressible by any such force as may be conveyed to it from the heart through the carotid and vertebral arteries. Upon the whole, then, I think we may assume the position as being in the highest degree probable, that, in the ordinary state of the parts, no material change can take place in the absolute quantity of blood circulating in the vessels of the brain.

Burrows in 1843 (5) was probably the first to question the absolute accuracy of this doctrine which so firmly considered the brain as of fixed incompressible bulk. He emphasized strongly the importance of the cerebro-spinal fluid, as the means of replacing the loss of blood during hemorrhage, for he felt that the amount of intracranial blood was obviously diminished by systemic bleeding.

"Whether the vacated space is replaced by serum, or resiliency of the cerebral substance under diminished pressure, is another question" was Burrows' summary of the possible readjustment for variations in the volume of the cerebral blood. As far as can be ascertained, this is the first statement of the view that the volume of the brain may be altered in accord with pathological or physiological conditions within the cranium. Burrows presents one of the most satisfactory conceptions of the whole process of fluid changes within the cranium (p. 32):

Those who have maintained this doctrine of the constant quantity of blood within the cranium, have not, I believe, taken into due consideration that large proportion of the contents of the cranium which consists of extra-vascular serum. Regarding this serum as an important element of the contents of the cranium, I admit that the whole contents of the cranium, that is, the brain, the blood, and this serum together, must be at all times nearly a constant quantity.

It was only when the subject of a constant blood volume in the cranium was subjected to experimental test that reliable data were obtained. Kussmaul and Tenner (6) demonstrated the unreliability of post-mortem observations and came to the conclusion, advanced by Burrows and supported by the experimental work of Donders (7), that variations in the total volume of blood in the cranium occurred. These early experiments, as pointed out by Leonard Hill (8) in 1896, are not conclusive as variation in the blood volume in one part of the cerebral vascular system might well be compensated by readjustments in another. Following many other investigators who used various methods of experimental attack, Leonard Hill concluded that (p. 77): "The volume of blood in the brain is in all physiological conditions but slightly variable."

More recently (1914) Dixon and Halliburton (9), in the course of an extensive study of the cerebro-spinal fluid, have come to the conclusion "that the cranial contents cannot any longer be regarded as a fixed quantity without the power of expanding or contracting in volume."

It must be assumed, however, that with certain reservations, the data favor the idea of a relatively fixed total volume of the cranial contents but with the capacity for change in any one of the three chief elements concerned.

The conception of a more or less constant cranial content is closely related to the questions which are naturally called forth by the experimental modification of brain bulk, detailed in foregoing sections of this paper. For within the closed cavity the alteration in volume of any element must be at the expense of the other elements. First of the possible explanations of the experimental alteration in brain bulk is that relating to the blood volume of the cranium. Are the vascular readjustments following the intravenous injection of hypotonic and hypertonic solutions sufficient to account for the definite change in brain bulk? In one of his original experiments, in which the cranium of a dog had been trephined. Kellie observed a recession of the brain away from the skull during exsanguination. Ecker (9) also observed in a trephined animal a remarkable shrinkage of the brain when the loss of blood from division of the carotids became excessive. The converse of this vascular diminution of the brain volume was recorded also by Ecker, who found that pressure on the thorax of a trephined dog caused protrusion of the brain into the cranial opening. Burrows also comments on this possibility of hernia through the trephine opening occurring in those cases in which the blood supply to the brain was markedly increased. These early observations on the relation of the cranial vascular supply to the volume of the brain during life have been confirmed and substantiated by many other workers on the cerebral circulation and cerebro-spinal (intracranial) pressure.

In our own experiments the modification of brain bulk has been produced both in the opened and in the intact skull. Observations on venous and arterial pressures under such experimental conditions have been made; these will be reported at another time. But that these alterations in brain bulk are independent of changes in volume of the blood in the vascular bed, may be deduced from other findings. The fact that similar changes occur in both the trephined and the unopened skull is strong evidence against the view that these changes in brain bulk depend on alterations in vascular volume and the persistence of the anatomical change after formalin fixation makes such a view untenable. For it must be assumed that with death of the animal, opening of the chest, introduction of a cannula in the aorta, injection of formalin through this vessel and release of the pressure by incising the right auricle, any vascular alterations existing in life are no longer maintained; so that the persistence, after such fixation, of a given brain bulk, if due simply to the amount of blood in the capillary bed and other vessels of the brain, would be impossible. That changes in

bulk do persist after fixation as above, is ample evidence that such changes are maintained by some fundamental and comparatively stable alterations in the substance of the brain itself. A further fact, which shows that the changes in volume of the brain as produced in these experiments are fundamentally independent of vascular alterations, is that brains fixed by immersion in formalin, as well as those preserved by arterial injection of the fixing agent, retain in part the changes in bulk produced by intravenous injection. Following several experiments in which, after opening of the skull the brain bulk was changed by intravenous injection, the heads of the animals were cut from the body and immersed in formalin. That the skull and dura were freely open during experimentation in these cases and that all the vessels of the neck were severed before fixation by immersion and not by injection and that after such treatment the brain still maintained the volume change brought about by the intravenous injection, are further evidence that the changes in bulk are independent of vascular alterations. While, as has been emphasized, the method of preservation does not accurately maintain the condition existing in life, it nevertheless makes possible the recognition of undeniable evidence of change in brain bulk. Vascular alterations may account for some changes in brain bulk which occur in the living animal, but the changes persisting in death and after the technical procedures employed in this investigation are quite evidently due to some other cause.

The other variable factor which may operate within the cranium in producing changes in brain bulk involves the cerebro-spinal fluid. We have already noted the lasting rise in the pressure of the cerebro-spinal fluid following the intravenous injection of a hypotonic solution, and the production of swollen brains by such injections. Conversely, a definite decrease in the size of the brain has been found in those cases in which the pressure of the cerebro-spinal fluid has been markedly lowered by intravenous injection of hypertonic solutions. In considering these results it becomes rather difficult to determine with absolute accuracy the primary factor involved in producing these alterations. Does the modification of the bulk of the brain determine the pressurechange in the cerebro-spinal fluid or are both dependent individually on some more fundamental cause? That change in brain volume in our experiments is not caused alone by changes in the pressure of the cerebro-spinal fluid is demonstrated by its occurrence in the opened skull, for with the trephine opening and the dura incised, the fluid pressure becomes minimal, and any rise in pressure is within certain limits

relieved. That fundamental osmotic changes in the blood are responsible for the changes in the pressure of the cerebro-spinal fluid, following intravenous injections of solutions of various tonicity, seems a reasonable conclusion. Although it is probable that change in the volume of the brain may affect the pressure of the cerebro-spinal fluid, and possible that changes in the pressure of the fluid may alter the bulk of the brain, in these experiments there is evidence that primary alterations in brain bulk and cerebro-spinal fluid pressure, both, are caused by fundamental osmotic changes in the blood supplied to the brain.

Such considerations force one to conclude that the alteration in the volume of the brain following intravenous injections of hypotonic or hypertonic solutions is quite independent of change in either the volume of the blood supply to the brain or of the pressure of the cerebro-spinal fluid. With the diminution in bulk the pressure of the cerebro-spinal fluid falls—a partial compensation for the evacuated space formerly occupied by the brain of normal size. Conversely, an increased bulk of the brain may cause dislocation of a certain volume of the cerebrospinal fluid, thus raising its pressure as determined in a manometer.

Relating this experimental modification of the brain bulk to the restricted Monro-Kellie doctrine it becomes evident that another variable factor must be introduced. The brain should no longer be considered as incompressible and of fixed volume as the early writers assumed it to be, but as subject to variation in size under experimental Monro, of course, qualified his theory by consideration of conditions. matter "effused or secreted from the blood vessels," and Burrows suggested that the brain possessed "resiliency of the cerebral substance under diminished pressure." Pathologically the increase in bulk of the brain is well known in the cerebral edemas of trauma, acute infections and certain other conditions. Similarly, pathological states characterized by diminished volume of the brain are also quite common. The Monro-Kellie doctrine then requires marked modification: the view so well advanced by Burrows is probably the more correct. This leads one to assume that the cranial cavity is relatively fixed in volume and is completely filled by brain, cerebro-spinal fluid and blood; variations in any one of the three elements may occur, compensation being afforded by alteration in the volume of one or both of the remaining elements.

The underlying processes involved in the modification of brain bulk by the intravenous injection of hypertonic and hypotonic solutions seem concerned then with osmotic changes in the blood. That the osmotic pressure of the blood is an essential factor in such experimental

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changes in brain bulk is shown by the fact that no alteration in the volume of the brain follows relatively large doses of Ringer's solution (100 cc. in a cat) but occurs promptly on intravenous injection of far smaller amounts of distilled water or concentrated salines. Just how this change in osmotic value of the blood affects the brain tissue and alters its volume can only be speculated upon at the present time. The change is limited apparently by the potential distensibility or contractility of the brain in the particular animal used. Thus, in old cats, the alterations in brain volume have not been so marked as in younger animals, though the contractility seems to persist longer than the distensibility. On the other hand, in young animals the change in cerebral volume is of far easier accomplishment. Capacity for osmotic changes in these animals must be about the same; the resultant modification of the brain bulk then is limited by anatomical factors. Finally, in the closed skull certain changes take place, limited by the potential powers of change in the brain itself and by the intradural capacity; in the trephined skull, the only limitation to change is the intrinsic capability for contraction or expansion of the brain itself.

SUMMARY

1. Intravenous injection of a hypertonic solution (30 per cent NaCl or saturated NaHCO₃) is followed by a marked decrease in size of the brain; when the skull is opened the brain may be seen to fall away several millimeters from the inner surface of the skull after such injection.

2. Intravenous injection of a hypotonic solution (water) causes a marked swelling of the brain; when openings are made in the skull the brain will rise, forming tense herniae protruding several millimeters through the trephine openings.

3. These changes are independent of the volume of the fluid injected and are probably due to fundamental osmotic effects of the hypotonic and hypertonic solutions.

4. The brains of old cats fail to respond readily to intravenous injection, particularly to the intravenous injection of hypotonic solutions.

5. Internal changes, recognizable histologically, have been found quite constantly in the brains of animals which have been given intravenous injections of hypertonic or hypotonic solutions and which have not been trephined. On the contrary, in animals in which the skull is opened and the brain thus allowed to change its volume freely, these histological changes have not been demonstrated.

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PLATE I

Fig. 1. Photograph $\times \frac{3}{4}$. Cat no. 1304. Adult female. Occipito-atlantoid puncture. Continuous observation of pressure of cerebro-spinal fluid for 75 minutes, with intravenous injection of 35 cc. sterile distilled water. Pressure rose from 105 mm. to 175 mm. following injection. Sacrificed with ether 30 minutes after completion of injection. Fixed by injection with 10 per cent formalin. Dura not removed.

Fig. 2. Photograph $\times \frac{3}{4}$. Cat no. 1371. Adult male. Intravenous injection of 20 cc. 30 per cent NaCl (Squibb) in 5 cc. doses given at 30 minute intervals. Sacrificed with ether 2 hours after first and 30 minutes after last dose. Fixed by injection with 10 per cent formalin. Dura not removed.

Fig. 3. Photograph \times 1. Cat no. 1402. Adult female. Control. Wellnourished, normal animal. Sacrificed with ether. Transverse section through optic chiasma. Fixed by injection with 10 per cent formalin.

Fig. 4. Photograph \times 1. Cat no. 1309. Young adult female. Occipitoatlantoid puncture. Continuous observation of pressure of cerebro-spinal fluid for 81 minutes, with intravenous injection of 12 cc. Ringer's solution. Initial pressure 90 mm., final pressure 110 mm. Sacrificed with ether 1 hour after completion of injection. Transverse section through optic chiasma. Fixed by injection with 10 per cent formalin.

Fig. 5. Photograph \times 1. Cat no. 1304. Transverse section through optic chiasma of brain shown in figure 1.

Fig. 6. Photograph \times 1. Cat no. 1371. Transverse section through optic chiasma of brain shown in figure 2.

Fig. 7. Photograph \times 1. Cat no. 1303. Adult female. Occipito-atlantoid puncture. Continuous observation of pressure of cerebro-spinal fluid for 84 minutes, with intravenous injection of 20 cc. sterile distilled water. Pressure rose from 106 mm. to 195 mm. Sacrificed with ether 1 hour after completion of injection. Transverse section through optic chiasma. Fixed by injection with 10 per cent formalin.

Fig. 8. Photograph \times 1. Cat no. 1364. Young adult female. Occipitoatlantoid puncture. Continuous observation of pressure of cerebro-spinal fluid for 90 minutes, with intravenous injection of 10 cc. saturated aqueous solution of sodium bicarbonate. Pressure fell from 115 mm. to below zero. Sacrificed with ether 70 minutes after completion of injection. Transverse section through optic chiasma. Fixed by injection with 10 per cent formaldehyde.

PLATE II

Fig. 9. Photograph $\times \frac{3}{4}$. Cat no. 1524. Adult female. Weight 2,350 grams. Temporal decompression on left side. Intravenous injection of 100 cc. sterile distilled water. Marked hernia of brain through trephine opening 3 mm. beyond outer table of skull beginning with the injection and persisting until animal was sacrificed with ether 35 minutes after completion of injection. Fixed by immersion with 10 per cent formalin. Trephine opening made on right side after the beginning of fixation. Fig. 10. Photograph $\times \frac{3}{4}$. Cat no. 1531. Adult male. Weight, 2,330 grams. Temporal decompression on left side. Intravenous injection of 100 cc. Ringer's solution. Brain lies convex with no hernia or evidence of swelling or shrinkage throughout the experiment. Sacrificed with ether 36 minutes after completion of injection. Fixed by immersion with 10 per cent formalin. Trephine opening made on right side 45 minutes after the beginning of fixation.

Fig. 11. Photograph $\times \frac{3}{4}$. Cat no. 1506. Adult male. Weight, 2,100 grams. Temporal decompression on left side. Intravenous injection of 16½ cc. 30 per cent NaCl (Squibb). Brain rises slightly with beginning of injection but falls away from skull before injection is finished. Thirty minutes later lies concave, 3 mm. below inner table of skull at forward edge of opening. Sacrificed with ether 33 minutes after completion of injection. Fixed by immersion with 10 per cent formalin. Trephine opening made on right side after the beginning of fixation.

Fig. 12. Photograph \times 1. Cat no. 1501. Adult female. Weight 2,400 grams. Temporal decompression on left side. Intravenous injection of 100 cc. sterile distilled water. Brain rises as injection begun; hernia increases during injection; brain bulges markedly through trephine opening with protrusion in center about 8 mm. beyond outer table of skull, 35 minutes after injection finished. Sacrificed with ether 37 minutes after completion of injection. Fixed by injection through aorta with 10 per cent formalin. Transverse section just behind optic chiasma. Dura removed.

Fig. 13. Photograph \times 1. Cat no. 1503. Adult female. Weight 2,260 grams. Control. Temporal decompression on left side. No intravenous injection. Brain lies convex about level with the outer table of the skull throughout experiment. Sacrificed with ether 35 minutes after completion of decompression. Fixed by injection through aorta with 10 per cent formalin. Transverse section just behind optic chiasma. Dura removed.

Fig. 14. Photograph \times 1. Cat no. 1505. Adult female. Weight 2,050 grams. Temporal decompression on left side. Intravenous injection of 16½ cc. 30 per cent NaCl (Squibb). Brain bulges markedly during injection, but immediately begins to subside on completion of injection until in 30 minutes it lies concave 1 mm. below inner table of skull. Sacrificed with ether 36 minutes after completion of injection. Fixed by injection through aorta with 10 per cent formalin. Transverse section just behind optic chiasma. Dura removed.

Fig. 15. Photograph \times 1. Cat no. 1536. Adult female. Weight 2,430 grams. Double temporal decompression. Intravenous injection of 100 cc. sterile distilled water. Beginning with the injection brain rises in a tense hernia on both sides. Sacrificed with ether 31 minutes after completion of injection. Fixed by injection through aorta with 10 per cent formalin. Transverse section through optic chiasma. Dura removed.

Fig. 16. Photograph \times 1. Cat no. 1532. Adult male. Weight 2,250 grams. Control. Double temporal decompression. No intravenous injection. Throughout experiment brain lies convex with no bulging. Sacrificed with ether 20 minutes after completion of decompression. Fixed by injection through aorta with 10 per cent formalin. Transverse section through optic chiasma. Dura removed. Fig. 17. Photograph \times 1. Cat no. 1541. Young male. Weight 1,500 grams. Double temporal decompression. Intravenous injection of 16 cc. 30 per cent NaCl (Squibb). Beginning with injection brain falls away from skull lying about 3 mm. below inner table 20 minutes after injection stopped. Sacrificed with ether 55 minutes after completion of injection. Fixed by injection through aorta with 10 per cent formalin. Transverse section through optic chiasma. Dura removed.

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PLATE 2





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16







(Weed and McKibben: Experimental alteration of brain bulk)

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hair from children in Costa Rica with the hair disturbances has been taken now and then to illustrate the progress of the return of pigment, but no controlled time measurements of growth were taken. Except for microscopic examinations, no special studies thus far have been made of these hairs. The scalp revealed slight pityriasis but no seborrheic dermatitis. Changes were observed sometimes in the eyebrows and eyelashes. As mentioned previously, associated cutaneous changes varied from normal skin to severe follicular keratoses and severe pellagrous dermatitis.

In general, records of the food intake of the children who exhibited such hair disturbances indicated a diet that consisted chiefly of bananas and molasses. Detailed analyses of the diets of these children will be published in subsequent reports.

In an effort to understand the background of these changes in the hair which would recede with improvement in the patient's general condition, various fractions of vitamin B complex were given in an uncontrolled fashion to the children. It had been observed previously that the hospital diet had effected a cure, unless the patient died shortly after admission or presented such severe reactions as diarrhea, edema, hepatosis or cirrhosis when the parenteral use of the vitamin fractions was necessary. Originally it had been planned to attempt to study the addition of such specific substances as inositol, calcium pantothenate, para-aminobenzoic acid and choline, alone and together with other fractions of the B complex. However, in addition to usual routine therapies biotin, without assay studies, was given orally, usually in doses of 0.25 mg. two or three times a day. With the addition of biotin, the return of both pigment and growth of the hair appeared to be accelerated definitely over that observed on a hospital diet or a hospital diet plus thiamine plus nicotinamide and other vitamins. These studies have been wholly uncontrolled: hence, the assumption of the more rapid action of biotin is purely an opinion and not a proved fact. Since similar cases of interesting changes in the hair are still available for additional studies, an effort will be made to determine, with due allowance for individual variations, the comparative accelerative effect of the various fractions of the B complex group.

CONCLUSIONS

In Costa Rica infants and young children with severe avitaminosis, especially vitamin A deficiency, pellagra, riboflavin deficiency, beriberi, nutritional edemas or mixed avitaminosis syndromes, have been observed to exhibit characteristic associated changes in the hair, both loss, diffuse or especially pronounced in the frontal area, and depigmentation. These changes in the hair resemble those reported previously by Trowell, Kark, Williams, Gillman and Gillman and others in the syndrome of infantile pellagra in South Africa. These changes are easily reversible if the patient survives the severe vitamin deficiency state. Improvement may be produced by a general, adequate diet if it is utilized alone or together with polyvitamin mixtures of the B complex.

The addition of biotin is thought, but not proved, to accelerate over other therapies the return of normal growth and pigmentation to the hair. Similar severe changes were not observed in the hair of adults with decided vitamin deficiency syndromes.

Clinical Notes, Suggestions and New Instruments

THE CONTROL OF BLEEDING DURING OPERATION BY INDUCED HYPOTENSION

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The olfactory groove meningioma is a benign tumor which arises from the midline of the floor of the anterior fossa of the skull, and its removal is beset with difficulties for the following reasons: First, the location of the tumor renders it relatively inaccessible; second, it is a large and vascular growth; third, its nutrient vessels come up through the base of the skull so that they are difficult to control until after the tumor is removed.

The best method of dealing with these tumors is to perform a right frontal craniotomy and to excise the portion of the right frontal lobe overlying the lateral aspect of the growth. With the electrosurgical unit the tumor is then removed in fragmentary fashion, after which the nutrient vessels in the floor of the skull at its area of attachment are treated by application of the cautery and bone wax. The loss of blood during operation may be severe. In many cases the surgeon makes extremely slow progress with the removal of the tumor until the patient's blood pressure falls as the result of loss of blood. After this occurs, bleeding from the cut surface of the tumor can be readily controlled, and the removal of the tumor goes on apace.

This was well illustrated by a patient who was operated on recently. The operation required three hours. In the first two hours less than one third of the growth had been removed. At this point the blood pressure fell from 130 to 80 because of loss of blood. Thereafter hemostasis was more readily effected, and the remainder of the tumor was quickly removed. Bleeding from the nutrient vessels coming up through the floor of the skull was then easily controlled by electrocautery, bone wax and pledgets of cotton soaked in thrombin solution. The patient received 1,500 cc. of blood during the operation, despite which the hemoglobin fell from a preoperative level of 12 Gm. to 8.9 Gm. forty-eight hours later.

For some years I have entertained the idea of lowering the patient's blood pressure by venipuncture during the first stage of these operations in order that bleeding from the tumor might be more readily controlled. Afterward the patient's own blood could be returned instead of transfusing blood from a donor. This method, however, has not been actually employed.

Kohlstaedt and Page¹ in 1943 in experiments with dogs described an ingenious method for the study of shock by arterial bleeding and infusion. Briefly, this method consists in placing a cannula in the femoral artery directed toward the heart. This cannula leads to a closed reservoir into which the dog is bled until the blood pressure is lowered to 30 mm. of mercury. The blood is mixed with an anticoagulant during its withdrawal. The arterial pressure is recorded on a kymograph. To raise the blood pressure the blood is infused into the femoral artery by the simple expedient of raising the pressure in the closed reservoir by pumping air into it.

This method permits the investigator to reduce the blood pressure to any desired level, hold it there as long as desired and then bring it back by infusion of the removed blood, provided, of course, that the animal is not permitted to go into terminal shock. In the treatment of hemorrhagic shock these authors found intra-arterial infusion more effective than intravenous.²

Page³ found that the intra-arterial infusion method for the treatment of shock has several advantages. "(1) The delivery

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of blood into the aorta perfuses the coronary vessels, relieving myocardial ischemia and, since myocardial ischemia probably underlies the cardiac dilatation and insufficiency, places the heart rapidly in a state in which it can pump the infused blood to other areas; (2) when, before the infusion, the patient may have been apneic, at its start he will take a deep breath, as if the arterial filling had rapidly extended to the vital medullary centers; (3) in contrast with intravenous transfusion, blood pressure is rapidly restored. . . ."

In its effect, therefore, intra-arterial infusion of blood may be said to furnish the patient in shock with an accessory heart.

REPORT OF CASE

On April 3, 1946 a woman aged 49 presented herself with a complaint of blindness. She was 5 feet 2 inches (157.5 cm.) tall and weighed 280 pounds (127 Kg.). The history showed loss of sense of smell for one year. Dizzy spells began in June 1945, and it was discovered at that time that she had hypertension. In November she experienced a period of unconsciousness lasting two days, followed by frequent severe head-aches and rapid failure of vision.

On examination the blood pressure was 200/130 mm. of mercury, which fell to 170/100 with rest in bed. The patient was tremendously obese, and there was bilateral optic atrophy



Page procedure for induced hypotension. A, cannula in left dorsalis pedis artery; B, arm to reservoir to receive arterial blood; C, arm to manometer; D, arm to syringe with heparin solution; E, air space above the blood connected to F, another manometer, and to G, a rubber bulb by means of which the pressure in E is raised or lowered at will.

with papilledema. She was able to see fingers with the right eye at 6 inches, and the left eye was totally blind. The sense of smell was completely absent. Roentgenologic examination of the skull showed some erosion of the posterior clinoid processes. The spinal fluid pressure was 450 mm. of water. The fluid contained 170 mg. of protein per hundred cubic centimeters. There was no evidence of renal failure. The possibility of malignant hypertension was at first entertained, but the diagnosis of olfactory groove meningioma soon became apparent.

Operation was performed on April 19. With the patient under pentothal sodium anesthesia, a cannula (A in the illustration) was placed in the left dorsalis pedis artery directed toward the heart. One arm (B) of this glass cannula led to the closed reservoir to receive the arterial blood. Another arm led to a blood pressure manometer (C), and a third arm (D) to a syringe containing heparin solution. The air space (E) above the blood in the reservoir was connected to another manometer (F) and to a rubber bulb (G) by means of which the pressure in the air space above the blood could be raised or lowered at will. Screw or pinch clamps were used at strategic positions to control the flow of blood.

While the scalp incision was being made, 1,600 cc. of blood was allowed to flow rapidly into the reservoir, and in fifteen minutes the intra-arterial pressure fell from 140 mm. of mer-

cury to 100. The pulse rate, which was 130 before bleeding, rose to 140. A right frontal craniotomy was performed, and the frontal lobe was elevated on a retractor. A large, soft, vascular meningioma was disclosed attached to the floor of the anterior fossa near the midline. In order to improve the surgical exposure the lower portion of the frontal lobe overlying the tumor was removed by block resection. The tumor was then removed in fragmentary fashion with the electrosurgical unit and by digital enucleation. The anterior portion was found to have straddled the crista galli and lower portion of the falx. Its posterior portion caused pressure on both optic nerves.

The tumor was extremely vascular, but despite this there was little loss of blood during the procedure. When arteries were divided, bleeding could be readily controlled by application of the electrocautery. In addition, it was noted that the blood clotted quickly, and the clot was quite firm. After removal of the growth the nutrient vessels in the floor of the skull at the area of the attachment of the tumor were readily controlled by electrocautery, and it was not necessary to use thrombin solution or bone wax to complete the hemostasis.

The pressure in the reservoir was then increased, and the patient's blood was infused into the dorsalis pedis artery. The operator waited until 1,100 cc. of blood had been infused before closing the wound. The infusion raised the intraarterial pressure from 90 to 120 mm. of mercury and resulted in some bleeding from the scalp incision but none from the tumor bed. The wound was then closed.

When the patient arrived at the ward the pulse was 120 and the blood pressure 150/100 mm. of mercury. The tumor in this case was removed more satisfactorily and with less bleeding than in any other case in the operator's experience. The total operating time was two hours and thirty-five minutes. The actual operating time was less, because the operation was suspended for about thirty minutes to watch for recurrence of bleeding in the tumor bed during the arterial infusion. The last 500 cc. of blood in the reservoir was discarded because it had clotted as a result of insufficient heparin solution. Despite this the hemoglobin on the fourth postoperative day was only reduced to 12.0 from a preoperative level of 13.3 Gm. Convalescence was smooth except for an unexplained low grade fever which persisted for eight days after operation. Because of this fever the patient was not discharged until the thirteenth postoperative day. She was last seen ten weeks later, at which time her progress was quite satisfactory. The vision was improving, and the blood pressure was 180/100 mm. of mercury.

The experience with this method in this 1 case, therefore, was certainly encouraging, and it seems that the procedure should be given a further trial.⁴

COMMENT

Page³ has shown that peripheral vasoconstriction is an early and constant accompaniment of shock. He has shown that during and for a short time after the initiation of shock this vasoconstriction is neurogenic due to vasomotor reflexes. As the brief period of nervous irritation passes off and unfiltrable substance appears in the plasma, which, when injected into the vessels of an isolated perfused rabbit's ear, causes severe and prolonged vasoconstriction. Thus, there is good reason to believe that the persistent nonneurogenic vasoconstriction in shock is due to the appearance of this substance in the blood. Evidence indicates that it is neither of renal nor of adrenal origin but arises from the site of tissue injury. We believe that it was chiefly this peripheral vasoconstriction rather than the reduction of blood pressure which was responsible for the ease with which hemostasis was obtained in the case reported. It is not necessary to reduce the blood pressure to a dangerously low level in order to bring the peripheral vasoconstrictor mechanism into play.

^{4.} Since its use in this original case the Page procedure or a modification of it has been employed in 6 additional cases with similar gratifying results.

SUMMARY

Hemostasis was aided during operation for brain tumor by preoperative arterial puncture and blood letting. The patient's blood was returned intra-arterially at the conclusion of the operation, thus avoiding the necessity of giving a transfusion.

DIFFUSE CALCIFICATION OF THE PANCREAS

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The presence of stones within the ducts of the pancreas has been recorded in the literature in 220 instances up to the year 1944.1 Diffuse calcification of the pancreas differs, in that the process of calcification is distributed throughout the organ, with associated destruction of the parenchyma. The organ may contain many cysts of varying size and much connective tissue; it may resemble a "bag of stones." 2 Beling 3 collected 12 reports of diffuse calcification and added 1 of his own. He and his associates later added another.⁴ King and Waghelstein ⁵ reported 4 instances of this disease. Reviewing the reports of Beling they disagreed with the diagnosis in 2 cases which they thought were questionable. Darling 6 recorded an instance of diffuse calcification of the pancreas observed in Australia. The case herewith reported brings the number to 18.

REPORT OF CASE

First Admission .- History: A white man aged 23 was admitted to the Santa Barbara Cottage Hospital in September 1944, referred to me by Dr. Artemas Strong of Santa Paula. Three years before he had been seized with "quite severe" epigastric pain over the upper half of the abdomen, associated with nausea, vomiting, diarrhea and a "low fever." He was ill for seven days. Over a period of two years similar pains occurred every four to six weeks; their duration was five to seven days. The only difference was the absence of diarrhea after the first attack. During the third year of his illness the "spells" occurred each four weeks. In 1942 a diagnosis of duodenal ulcer had been made elsewhere and confirmed by roentgen ray. He was placed on a plain diet with milk. His pain continued.

On hospitalization in August 1944 he stated that he was nauseated by all foods excepting bouillon and so had taken only that. His weight in six months had gone from 143 to 118 pounds (65 Kg. to 54 Kg.), a loss of 25 pounds (11 Kg.). His height was 5 feet 4 inches (163 cm.). He had been having daily two loose, not watery, dark brown stools. The urine was straw colored. Jaundice had not been observed.

For the past two years he had been a sprayer in a lemon orchard, using arsenate of lead. He smoked half a package of cigarets a day and used alcohol regularly, occasionally becoming intoxicated.

Examination: Examination revealed a dehydrated, acutely ill man, who seemed older than his 23 years. The tongue was dry and red, the gums boggy and bleeding and the teeth in need of repair. A lead line was absent. The blood pressure was 122 systolic and 70 diastolic. The abdomen was moderately distended; there was much tenderness throughout the upper quadrant and the left lower quadrant. Rebound tenderness was present over the left upper quadrant. The temperature was 100 F. the first day after admission, 99 F. the second and normal or lower thereafter.

Laboratory Observations: On examination of the blood, the sedimentation rate was 20 mm. in sixty minutes (Cutter);

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6. Darling, H. C. R.: A Case of Progressive Calcification of the Pancreas Secondary to Chronic Relapsing Pancreatitis, M. J. Australia 2:7 (July 4) 1942.

hemoglobin 77 per cent (11.7 Gm.); erythrocytes 3,600,000; leukocytes 7,800, with polymorphonuclears 82 per cent and lymphocytes 18 per cent. No basophilic punctation was found. The stools were loose and dark brown, with 4 plus occult blood present.

Roentgenologic Observations: The stomach was dilated and contained fluid. The duodenal bulb was decidedly irritable and retained its barium poorly. There was pronounced segmentation of the barium mixture in the jejunal coils. After four hours there was a 60 per cent retention of barium in the stomach. The diagnosis was obstructive duodenal ulcer, deficiency state. Films of the right upper quadrant after the oral administration of priodax showed a well filled gallbladder; adequate contraction occurred under the stimulus of a fat meal. There was no evidence of calculus.

Treatment: The patient was placed on Sippy ulcer management, and he returned home.

Second Admission .- History : He was readmitted to the hospital four months later, at which time he stated that after the institution of ulcer management he was free of symptoms for



Shadows indicating calculi in the head of the pancreas and extending across the spine into the tail.

four weeks. Pain then recurred; it started on the left side of the abdomen in the upper quadrant, radiating downward on the same side of the abdomen and down the inner side of the leg. The pain was constant, with exacerbations of severe pain which required hypodermics of morphine sulfate for relief. When not given the drug the patient walked and moved about continuously. If he sat in the same position for fifteen minutes the pain returned. He also complained of constant tenderness in the left side of the abdomen. His appetite was poor, and he had been nauseated and had vomited every morning for the past month.

Examination: Persistent spasm was present on the left side in both the upper and lower quadrants of the abdomen, most pronounced over the left upper quadrant. The oral temperature varied from 99 to 99.2 F.

Laboratory Observations: The laboratory work on this admission included examinations of the blood. The sedimentation rate (Cutter) was a 5 mm. fall in 60 minutes; amylase 68 units; nonprotein nitrogen 25 mg. per hundred cubic centimeters; hemoglobin concentration 90 per cent (15.1 Gm. per hundred cubic centimeters); erythrocytes 4,500,000, and leukocytes 6,300. The percentages of the various types of leukocytes

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THE EFFECTS OF ACTIVE AND PASSIVE HYPERVENTILATION ON CEREBRAL BLOOD FLOW, CEREBRAL OXYGEN CONSUMP-TION, CARDIAC OUTPUT, AND BLOOD PRESSURE OF NORMAL YOUNG MEN¹

BY SEYMOUR S. KETY AND CARL F. SCHMIDT

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(Received for publication July 19, 1945)

The physiological effects of hyperventilation, long a subject of considerable interest to clinicians as well as physiologists, recently assumed a new practical importance in connection with military aviation. Here, in numerous situations, overbreathing may be encountered because of emotions or pain, or it may be induced voluntarily, and the results may be favorable or unfavorable, depending on circumstances. At altitudes at which anoxemia can be completely prevented by inhalaof O₂, hyperventilation not only would exhaust the available supply of O_2 at an unduly rapid rate, but also would have an adverse effect on the ability of the flyer to meet the exigencies of combat aviation (1, 2). But, at altitudes above 35,000 feet, where inhalation even of 100 per cent O₂ cannot keep the alveolar oxygen tension from falling below the sea level normal, anoxemia can be prevented only by raising the pressure of the inhaled gas above the ambient pressure, or by making room for more O₂ in the alveoli by blowing off CO₂. If equipment for the former of these alternatives is not available, proves insufficient, suddenly becomes ineffective, or must be abandoned, the second may be the only possible means of avoiding incapacitating anoxemia. The relative dangers of anoxemia and acapnia then become a matter of immediate practical importance in connection with flight at extreme altitudes. If the cabin of the airplane is pressurized, the possibility of sudden decompression or the necessity for abandoning the plane at an altitude at which hyperventilation may be necessary for survival, must always be borne in mind. If the plane is not pressurized the altitude tolerated by the flyer might be increased, or the time during which he could take effective action at a given high altitude might be prolonged, by means of hyperventilation. Finally, the flyer's ceiling can be increased by simply raising the pressure of O_2 in the mask to a level higher than the ambient pressure, and this can be done by application of the added pressure either continuously or intermittently. The latter procedure is less uncomfortable than the former, but it is likely to cause considerably more hyperventilation.

For these reasons, not only the training of personnel for flight at extreme altitudes, but also the selection and procurement of equipment for such flight have called for fairly exact information concerning the physiological derangements brought about by hyperventilation. Meanwhile the importance of the same considerations in relation to the use of mechanical resuscitating devices has increased not only because of the greater need for resuscitation in connection with the current vogue of intravenous anesthesia, but also because of the recent availability of a number of more efficient devices for this purpose. Although a large amount of experimental work has been done in this field, both on laboratory animals and on man, the data hitherto available are not adequate for the present purpose. Thus, although passive hyperventilation is known to cause a profound fall in blood pressure in anesthetized animals (3) and man (4), due presumably to a decrease in vasomotor tone, voluntary hyperventilation by unanesthetized subjects apparently has no such effect (5). Whether this difference is due to the anesthetic or to the exercise involved in the voluntary process is unknown. Corresponding statements can be made

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about the effects on cardiac output, on which little information is available (6). One of the important effects claimed for hyperventilation is constriction of cerebral blood vessels, but the methods used to demonstrate this in man (increase in the femoral artery—internal jugular vein oxygen difference (7), increase in temperature in an artificially heated thermocouple inserted into an internal jugular vein (8), and decrease in the rate of displacement of cerebrospinal fluid during obstruction of both jugular veins in the neck (9)) are all open to criticism (10).

With the recent development of a method for measuring quantitatively the volume of blood flowing through the brain of an intact unanesthetized man (11), together with the ballistocardiographic method for estimating cardiac output (12) and standard means for determining arterial blood pressure, we had at our disposal for the first time the implements for securing unequivocal evidence on all of the points mentioned above. We could also calculate the amount of O_2 used by the brain from the cerebral arteriovenous O₂ difference, once the volume of cerebral blood flow was known. The total O₂ uptake was readily measured, and the proportion of this represented by cerebral metabolism then could easily be determined. The corresponding figure for the proportion of cardiac output represented by total cerebral blood flow also could be computed from the ballistocardiogram and the measured volume of cerebral blood flow.

We have carried out these measurements in normal young men in the recumbent position at sea level and under 3 conditions, viz., at rest, during voluntary hyperventilation, and during approximately equal hyperventilation produced by a positive pressure resuscitating device, the General Electric Pneumolator. The experiments have been extended subsequently to conditions other than hyperventilation, which was chosen for first study because of the possible immediate military value of the information.

METHODS

Subjects. These were normal young men (conscientious objectors) 23 to 31 years of age. They reported about 9 A.M., without breakfast, and lay quietly on the ballistocardiographic bed for approximately an hour before the experiment began. Seven different subjects were used but complete data (*i.e.*, under the 3 conditions noted above) could be obtained only in 5.

Cerebral blood flow measurements. The nitrous oxide method was used substantially as already described (11), the concentration of N₂O in the inhaled mixture being 15 per cent and that of O₂ 21 per cent in all cases. The balance was nitrogen. The period of measurement was 10 minutes. Samples of femoral arterial, and internal jugular venous blood were collected at 1, 3, 5, and 10 minutes after the start of the N₂O inhalation, the collections being accurately timed and synchronized. One such set was collected during quiet breathing, another (after about 5 minutes of quiet breathing and 10 minutes of hyperventilation with room air) during voluntary or passive hyperventilation. The other type of hyperventilation was tested on another day, after a rest period of 2 weeks or more. Each set of observations during hyperventilation, therefore, had its own set of control measurements during quiet breathing. Calculation of cerebral blood flow was carried out from the cerebral arteriovenous N2O difference substantially as described in our earlier report (11). The $\int_{a}^{t} (A - V) dt$ was measured simply from the area between the arterial and venous curves for N₂O content, thus avoiding any assumptions as to the shape of these curves.²

Cardiac output. The horizontal ballistocardiograph was used (12). Records were made as follows: (1) after the subject had rested for about an hour and before the needles had been inserted; (2) during the last 5 minutes of the control cerebral blood flow determination; (3) during the last 5 minutes of the cerebral flow determination during hyperventilation; (4) during the minute immediately following discontinuance of passive hyperventilation. The calculations of cardiac output from these records have been corrected for dimensions of the living aorta (13). The complexes were distorted at the start of the inspiratory phase of breathing during passive hyperventilation, and the measurements were made from parts of the tracing that were free from obvious artefacts of this character.

Blood pressure. The femoral arterial needle was connected to the manifold, containing the battery of syringes used for collecting blood samples, by an annealed silver tube provided with an extra opening to which a mercury manometer was connected. This was heavily damped and was used for the direct measurement of mean blood pressure. Systolic and diastolic pressures were also estimated in the arm by the usual auscultatory method. These measurements were made at about the same time as the ballistocardiograms.

Oxygen consumption. This was estimated from a spirogram made with a conventional small basal metabolism

² In some of the most recent experiments, it has been found that all assumptions as to the shape of the curves during the first minute of N₂O inhalation can be avoided by taking an additional pair of samples at a slow constant rate throughout this period. The arteriovenous N₂O difference in this pair immediately gives $\int_{a}^{1} (A - V)dt$.

outfit over a period of 3 to 5 minutes immediately after the period of measurement of cerebral blood flow. During hyperventilation, these spirograms were too erratic to yield valid measurements of oxygen consumption.

Pulmonary ventilation. The spirograms from which oxygen consumption was measured gave reasonably accurate information on this point during quiet breathing and voluntary hyperventilation. During passive hyperventilation, the corresponding measurements were attempted by noting the time required for the exhalation of 65 liters into an accurately balanced spirometer. This method proved unsatisfactory because of a slight but steady leak of gas through the pneumolator during a considerable though variable part of the expiratory phase. Consequently, we have no data on this point.

Collection and analysis of blood samples. Steel needles of 18 gauge were introduced into an internal jugular vein and a femoral artery after infiltration of the tissues with 1 per cent procaine. They were filled with sterile heparin solution (Abbott) by means of a syringe and promptly connected to the tube and manifold system. The latter was provided with a heparin-containing syringe by means of which fresh blood was drawn into relation with the collecting syringe just before the sample was collected and was replaced with a heparin-blood mixture just afterward. The usual aseptic precautions were observed throughout. The syringes used to collect the samples were of 10 ml. size, all glass construction. Each contained a mercury seal amounting to about 1 ml. and a little heparin. After some early experiments showed extraordinarily low figures for arterial pH and pCO₂, we took special pains to be certain that all traces of acid were removed from the freshly washed mercury before it was used.

The blood samples, measuring about 6 to 8 ml. and rendered incoagulable with heparin, were analyzed for N₂O content by the method previously used (11) and for O₂ and CO₂ content by the manometric method of Van Slyke (14). Separate 2 ml. samples were used for N_2O . Analyses for O₂ and CO₂ were made on at least the first and last pair of samples of each cerebral flow determination, and the values reported represent the respective averages. The hydrogen ion concentration of the samples was determined on the whole blood by means of a Mac-Innes-Belcher glass electrode and a Leeds and Northrup electronic potentiometer. These readings were made at 38° C., and with their aid it was possible to calculate the CO_2 tension (pCO₂) by means of the nomograms of Peters and Van Slyke (14). The blood samples were kept on ice between the time of collection and the time of completion of the analyses. The estimations of O₂, CO₂ content, and pH were begun at once, and all analyses were completed within 12 hours of the collection of the sample.

Other observations. In every experiment, attempts were made to determine the degree of mental alertness by noting the responses to questions and by observing the promptness with which instructions were followed. Signs of tetany were watched for during hyperventilation. The presence of indwelling needles in the internal jugular vein and the femoral artery precluded the use of the usual tests for cerebral functions.

The course of a typical experiment was as follows: The subject, who had had no food since the preceding evening, clad himself in light operating clothes and lay down on the ballistocardiographic bed. About an hour later ballistocardiogram I was recorded. The face mask was then applied and connected to a T-piece through which instantaneous shift could be made between ambient air and the N₂O-O₂-N₂ mixture. The needles were then inserted in the jugular vein and femoral artery and connected to their respective manifolds. The subject was assured that no other disquieting procedures would be carried out and the first (control) 10-minute period of measurement of cerebral blood flow was then begun; after the pair of blood samples had been collected at 5 minutes. the ballistocardiogram and blood pressure measurements were repeated. After the final (10-minute) pair of blood samples was collected, the inhalation of N₂O was discontinued in favor of room air, and when a few more minutes had elapsed, the control spirogram was made. Following this, hyperventilation with room air was begun and was continued for 10 minutes. Voluntary hyperventilation was carried out in time to a bell ringing every 10 seconds, the subject being instructed to take a comfortably deep inspiration and to exhale at a rate that would complete the cycle before the next signal. Passive hyperventilation was carried out with a positive pressure of 150 mm. (6 inches) H₂O which was found by experience to produce about the same degree of alkalosis as the described voluntary procedure. The gas used for this purpose was ambient air compressed in tanks of the same type as those containing the N₂O-O₂-N₂ mixture. At the end of this 10 minutes of hyperventilation with air, an extra sample of jugular blood was collected to give the base-line for the next N₂O period. Then the N₂O-O₂-N₂ mixture was substituted for room air, and the second period of blood flow measurement was begun; the hyperventilation was maintained as nearly constant as possible during this time. Again the ballistocardiographic and blood flow estimations were carried out during the latter 5 minutes of this period. At the end of this time, room air was substituted for the N₂O-O₂-N₂ mixture with the hyperventilation continuing as nearly constant as possible, and the second spirogram was made. Then the hyperventilation was discontinued, and the subject was instructed to relax completely. Usually, there was a brief apnea at this time and in some cases another ballistocardiogram was made as the subject began to breathe again. The total elapsed time was about 3 to 31/2 hours, of which about half was comprised in the periods of experimental observations. The hyperventilation period lasted 20 to 30 minutes; hence, the voluntary hyperpnea had to be only of moderate intensity, which the passive process was adjusted to resemble.

RESULTS

The essential data from 12 successful experiments are presented in Tables I, II, and III, and

<u>2008</u>	U.	Pu	lmo- ary	BI	ood C(D2 cont	ent	Cer A diffe	ebral V renc e	B	lood C	2 cont	ent	Cer A diffe	ebral -V erence	Cer	ebral		Bloo	d pH	
Su	lbject	venti	lation	Art	erial	Inte jug	ernal ular	С	02	Art	erial	Into jug	ernal Jular		D 2	K	. Q .	Art	erial	Inte ji g	ernal ular
		С	н	с	н	c	н	с	н	С	н	c	н	с	н	с	н	с	н	с	н
		liter mit	s per sute	v	olumes	per cet	nt	volu per	imes cent	v	olumes	per ce	nt	volı per	imes cent						
Active hyper- ventilation	S. H. A. C. L. E. M. H. D. M. W. H. W. G.	8.2 8.6 7.0 7.9 7.5 9.1	25.3 12.1 12.3 7.6* 15.2 20.2	51.4 51.7 49.4 52.2 49.1 50.0 51.1	37.9 42.5 41.9 48.7 39.3 40.5 45.1	55.4 55.6 54.5 58.4 53.8 55.0 57.3	47.7 53.9 52.8 58.0 49.1 51.6 55.7	4.0 4.0 5.1 6.2 4.7 5.0 6.2	9.8 11.4 10.9 9.3 9.8 11.1 10.6	17.0 17.8 17.5 17.0 18.7 18.5 18.0	18.4 18.8 17.4 17.6 19.4 19.4 18.8	11.0 12.0 11.8 10.9 12.6 12.1 11.4	9.4 8.2 6.6 8.1 8.4 8.4 7.8	6.0 5.8 5.7 6.1 6.1 6.4 6.6	9.0 10.6 10.8 9.5 11.0 11.0 11.0	0.67 0.69 0.90 1.02 0.77 0.78 0.94	1.09 0.98 1.01 0.98 0.89 1.01 0.97	7.30 7.29 7.39 7.43 7.38 7.39	7.44 7.52 7.52 7.53 7.57 7.56	7.36 7.41 7.35 7.34	7.46 7.45 7.46
H	Mean	8.1	15.5	50.7	42.3	55.7	52.7	5.0	10.4	17.8	18.5	11.7	8.1	6.1	10.4	0.82†	0.99	7.37	7.53	7.36	7.46
[Passive hy- erventilation	S. H. L. E. M. H. D. M. W. H.	6.5 8.1 6.8 6.5 7.8		45.7 51.1 49.2 49.7 50.5	37.4 40.1 44.3 41.4 40.8	53.2 58.4 55.7 56.0 57.9	48.3 52.1 54.7 53.7 51.8	7.5 7.3 6.5 6.3 7.4	10.9 12.0 10.4 12.3 11.0	17.7 17.6 16.7 19.8 18.2	18.5 18.7 17.2 20.1 18.8	10.6 9.4 9.5 13.0 11.5	7.8 7.0 6.3 7.6 7.7	7.1 8.2 7.2 6.8 6.7	10.7 11.7 10.9 12.5 11.1	1.05 0.89 0.90 0.93 1.10	1.02 1.03 0.96 0.98 0.99	7.43 7.42 7.35 7.37 7.38	7.58 7.60 7.50 7.51 7.63	7.42 7.34 7.30 7.31 7.34	7.49 7.49 7.40 7.58
= =	Mean	7.1		49.2	40.8	56.2	52.1	7.0	11.3	18.0	18.7	10.8	7.3	7.2	11.4	0.97	1.00	7.39	7.56	7.34	7.49

			TA	ABLE I			
Effects	of active at	nd passive h	yperventilation	on arterial	and cerebral	venous bloo	d constituents

C = control. H = hyperventilation. R.Q. = respiratory quotient. Further data in Table III. * This subject became drowsy during the period of hyperventilation and had to be reminded regularly of what was expected of him. Even though the respiratory minute volume seems to have decreased there was, by virtue of the slower and deeper respiration in this period, a real increase in effective ventilation as shown by the blood changes. † In this group of determinations oiled syringes were not used with consequent slight loss of CO₂ sufficient, however, to depress the R.Q. in some cases. This defect was corrected in subsequent experiments.

			Stroke	volui	me		Cardia	c out _f	out		Puls	e rate		b	dean a lood p dir	arteria pressui ect	l e	Auscu	ltatory blo	ood pressur	re
S	ubject	I	п	111	IV	I	п	111	IV	I	11	ш	IV	I	п	111	IV	I	II	111	IV
			,	nl.		li	ters pe	r min	ule						mm.	Hg			<i>mm</i> . 1	Hg.	
ctive hyper-	S. H. A. C. L. E. M. H. D. M. W. H.	77 72 71 70 68	76 63 70 69 74	75 56 70 64 60		5.5 6.5 5.8 4.1 4.5	4.9 5.2 4.9 4.5 4.9	5.6 5.3 4.6 3.8 5.7		72 90 82 58 66	64 82 70 65 66	75 94 65 59 95		83 92 90	86 88 95 86	97 96 93 97 93 112		118/70 105/78	117/80 105/78 112/80 100/70	130/95 120/70 105/90 100/74 135/105	
IA	Mean	72	70	65		5.3	4.9	5.0.		74	69	78		8	8	98		110	/76	118/87	
II Passive hy- perventilation	S. H. L. E. M. H. D. M. W. H. Mean	68 71 70 74 76 72	63 63 70 70 70 70	49 55 53 65 53 55	62 63 53 71 62	3.6 5.4 4.5 5.7 4.3 4.7	3.4 5.3 4.2 4.9 4.5 4.5	3.1 4.3 3.8 4.8 3.8 4.0	3.4 4.8 3.9 5.1 4.3	53 76 64 77 56 65	54 84 60 70 65 67	64 79 71 74 71 72	55 76 73 72 69		85 94 84 94 104 92	86 95 91 99 125 99	-	95/75 105/80 107	95/65 110/65 112/85 115/95 /78	90/70 105/75 102/95 120/95 104/84	

TABLE II

Effects of active and passive hyperventilation on cardiac output, pulse and blood pressure

I = control period (just before start of control blood flow measurement); II = latter 5 minutes of period of control blood flow measurement; III = latter 5 minutes of period of blood flow measurement during hyperventilation; IV = during first minute after cessation of hyperventilation.

EFFECTS OF ACTIVE AND PASSIVE HYPERVENTILATION

							-												
				•		Bloo	od CC	2 ten	sion	0		Basal	Me	ean,		Cere	bral		
		Age	Weight	Height	Sur- face area	Arte	erial	Inte	rnal ular	out	diac put	tabo- lism	blo pres	ood sure	Blo	bod w	O2 c sum	con- ption	Other effects
Su	bject					с	н	С	н	с	н		с	н	с	н	С	H	
		years	pounds	inches	m ²		mm.	Hg		lit p mir	ers er 1ule	ml. of O2 per minute	mm	. Hg	ml.	per 1 per m	00 gr uinute	ams	
	S. H.	24	147	69.5	1.82	52	31			4.9	5.6	300	83	97	59	44	3.5	4.0	Lost consciousness at 18' of H. Facial twitchings. Emo-
yperven. on	A. C. L. E. M. H.	23 26 25	147 148 160	69 70 69.5	1.80 1.83 1.85	55 43 41	28 29 32	49 48	43	5.2 4.9 4.5	5.3 4.6 3.8	244 252 310	86 92 88	96 93 97	87 70 56	51 40 48	5.0 4.0 3.4	5.4 4.3 4.6	tional upset afterwards.
ctive h tilati	D. M.	31	160	70	1.88	44	24	49	38			245	95	93	69	40	4.2	4.4	Clouded consciousness. Twitchings of head and ex- tremities.
IA	W. H. W. G.	23 23	155 150	73 70	1.91 1.83	43	25	50	38	4.9	5.7	252	86	112	79 73	52 53	5.1 4.8	5.7 5.8	Severe carpopedal spasm.
	Mean					46	28*	-50	40*	4.9	5.0	268	88	98	70	47*	4.3	4.9*	
iyper- on	S. H. L. E. M. H.	24 26 25	147 148 165	69.5 70 69.5	1.82 1.83 1.90	38 42 46	22 23 30	43 54 57	34 36	3.4 5.3 4.2	3.1 4.3 3.8	246 279 243	85 94 84	86 95 91	59 62 72	40 44 47	4.2 5.1 5.2	4.3 5.1 5.1	Clouded consciousness to- ward end of hyperventila-
assive l entilati	D. M. w н	31	165	70 73	1.91	45	27	56 55	45	4.9	4.8	218	94	99	81	40	5.5	5.0	tion. Lost consciousness toward end of hyperventilation. Carponedal spasm
II A	Mean					43	24*	53	36*	4.5	4.0*	248	92	99	66	41*	4.7	4.7	

TABLE III

Effects of active and passive hyperventilation on cerebral blood flow and cerebral oxygen consumption

C = control. H = hyperventilation.

* This represents statistically significant changes.

TABLE IV Percentile changes induced by active (A) and passive (P) hyperventilation

			Art	erial			Inte jug	ernal ular			Cere	ebral			Car	diaa	D1	
Subject	CO2 c	ontent	pC	01	(H	[+)	ρC	201	A diffe	-V rence	Blood	l flow	O2 uj	otake	out	put	pres	sure
·	A	P	A	P	A	Р	A	P	A	Р	A	Р	A	Р	A	P	A	Р
S. H. L. E. M. H. D. M. W. H.	-26 -15 -7 -20 -19	-18 -22 -10 -17 -19	-40 -33 -22 -45 -42	-42 -45 -35 -40 -50	-28 -27 -19 -36 -32	-30 -34 -29 -28 -45	-10 -22 -24	$-21 \\ -33 \\ -20 \\ -45$	+50 +90 +56 +80 +72	+51 +43 +52 +84 +66	-25 -43 -14 -42 -34	-32 -29 -35 -51 -34	+14 + 7 +35 + 5 +12	$+2 \\ 0 \\ -2 \\ -9 \\ +8$	per m + 14 - 6 - 15 + 16	ninute - 9 -19 -10 - 2 -15	+17 + 1 + 10 - 2 + 30	+ 1 + 1 + 1 + 8 + 5 + 20
Mean	-17	-17	-36	-43	-28	-33	- 19	- 30	+70	+59	-32	- 36	+15	0	+ 2	-11	+12	+ 8

A = active (voluntary). P = passive (pneumolator).

the most significant effects of hyperventilation are summarized in Table IV. The gaps in the tables are due to lack of pertinent information for various reasons. The estimations of pH and pCO_2 in the blood in the first 2 experiments (Tables I and III) were invalidated by failure to wash the mercury completely free of acid after cleansing it in towers of dilute nitric acid and distilled water in the usual manner; as a result, the pH values were abnormally low, but this oversight was remedied for the subsequent experiments. The relatively high values for arterial CO_2 content and tension during quiet breathing (Table I and III) are most probably referable to the dead space of the mask. The actual figures for the N_2O content of the various blood samples are omitted from the tables for the sake of simplicity, but representative examples are shown in Figure 1.

The intensity of the hyperventilation can be judged better from the changes in CO_2 content and acidity of the arterial blood than from the figures given for pulmonary ventilation. This is glaringly evident in the case of active hyper-



FIG. 1. NITROUS OXIDE CONCENTRATION CURVES FOR ARTERIAL AND INTERNAL JUGULAR BLOOD FROM WHICH CEREBRAL BLOOD FLOW IS CALCULATED

Two typical experiments on the same subject (D. M.) performed 3 weeks apart are illustrated. There is a lapse of about 20 minutes between the control and hyperventilation periods, during which nitrous oxide is cleared completely from arterial and almost completely from cerebral venous blood. Cerebral blood flow is calculated as previously derived (11) from $\frac{100 S(V_{10} - V_0)}{\int_0^{10} (A - V)dt}$ the constant S being a partition coefficient for nitrous oxide between brain and blood. It is apparent by inspection that during hyperventilation, the area between the arterial and venous curves $(\int (A - V)dt)$ increases considerably indicating a decrease in cerebral blood flow.

ventilation by M. H. (Table I), which indicates that the values listed for pulmonary ventilation should not be regarded as precise criteria of the degree of alkalosis involved in these experiments. The reason for this discrepancy is our practice of measuring the ventilation at a period different from that involved in the collection of the blood samples. The degree of voluntary hyperventilation could not be kept constant throughout the entire period which lasted more than 20 minutes. In the case of passive hyperventilation, we have to depend entirely on the blood changes for orientation on this point.

DISCUSSION

The data presented in the tables afford a considerably deeper insight into the physiological readjustments evoked by hyperventilation in normal man than had been possible hitherto because they include actual figures for the behavior of cerebral blood flow. They also permit a set of calculations, previously impossible, of the fractions of the total cardiac output and total oxygen consumption that are accounted for by the blood flow and oxygen uptake of the brains of normal intact men. The importance of each of these items of information is attested by the existence of a considerable literature bearing upon it. We believe, therefore, a full discussion of an interpretation of the probable significance of our findings to be justified.

The validity of these findings rests upon the competence of the methods employed. With the exception of the measurements of cerebral blood flow and cardiac output, these were standard procedures that call for no further comment. Our method for measuring cerebral blood flow, as pointed out elsewhere (11), has been subjected to calibration against direct measurement of cerebral blood flow in monkeys and has back of it, therefore, an assurance of fundamental accuracy that is rare among methods advanced for clinical use. Further experience with the method has led to several improvements in detail but to no fundamental change in principle or interpretation. The ballistocardiographic method for measuring cardiac output has been considered in detail in a recent symposium (15) where a full account of its strengths and weaknesses was presented. The

consensus appears to be that the results obtained are probably trustworthy, provided that neither hypotension nor tachycardia is present. Our experiments clearly fall into this category.

Changes in composition of blood. The actual data are given in Table I, and the percentile changes are summarized in Table IV. The most significant findings are those for cerebral arteriovenous differences for O₂ and CO₂, which underwent a consistent and considerable increase during hyperventilation of either type. Since mean blood pressure never fell and usually rose at the same time (Table II), this particular effect cannot be ascribed to depression of the general circulation but must have been due either to an increase in the rate of cerebral metabolism, or to an intrinsic diminution in the volume of blood passing through the brain, *i.e.*, cerebral vasoconstriction, or perhaps to both. The data shown in Table III indicate that the second of these was the dominant factor. These findings and their interpretation are fully confirmatory, therefore, of those of others (7, 25, 26).³ The indicated diminutions in CO₂ content and hydrogen ion concentration in both arterial and venous bloods are as expected, as are also the slight increases in arterial O₂ content (in view of the high resting arterial CO₂ content, which was attributed to the dead space of the mask).

The behavior of the cerebral respiratory quotient deserves a brief comment. This factor was practically the expected 1.0 in all cases except 4 out of the first series of resting (control) observations (Table I). The first 2 of these probably can be discounted because they were the instances of failure to remove all traces of acid from the mercury used to seal the syringes. The other 2 may have been related to the avoidance of oil to lubricate the syringes for fear that it would dissolve significant amounts of N₂O out of the blood samples. After these low values were obtained, we investigated this possibility and found it to be insignificant. From this time on, the syringes were lubricated and no more low respiratory quotients were obtained. The behavior of CO_2 naturally was not as important for our purposes as was that of N₂O.

Cerebral blood flow. The data are presented in Table III and are expressed on a percentile basis in Table IV. Without exception, cerebral blood flow diminished during hyperventilation. The degree of the change is somewhat surprising when it is remembered that these hyperpneas were only moderately intense. Definite signs of tetany were seen in only 4 of the 11 experiments and in only 3 of the 7 subjects, which may be taken as evidence that we were not dealing with an extreme alkalosis or acapnia. Yet the diminutions in cerebral blood flow during voluntary hyperpnea ranged from 14 to 43 and averaged 32 per cent, while during passive hyperventilation, the corresponding range in the same subjects was 29 to 51, and the average was 36 per cent. A change of this magnitude can scarcely be ignored in allocating responsibility for deterioration in cerebral functions during hyperventilation. As shown in Table III, signs of impairment of cortical activity were evident during hyperventilation in 5 of the experiments even by the crude methods which we used to detect such changes. The use of more exact tests for cerebral performance was precluded by the experimental conditions (particularly the indwelling needles and the mask).

The possible effects of hyperventilation on cerebral functions are so numerous and so poorly understood that it is impossible at present to evaluate the part played by any single factor with even approximate accuracy. Alkalosis, diminution in pCO_2 , changes in the cerebral O_2 -glucose ratios and respiratory quotients, all are elicited concurrently during hyperventilation (25, 26), and there is insufficient evidence by which to assess the relative importance of any of these. One group has found during hyperventilation a better correlation of electroencephalographic patterns and impaired consciousness with lowered pCO₂ in the internal jugular vein than with lowered pO_2 (25, 26). Nevertheless, it seems to us that a diminution in cerebral blood flow of the order of 30 per cent, while cerebral O₂ consumption is unchanged or increased (Tables III and IV), should

⁸ It is noteworthy, however, that actual calculations of cerebral metabolism in these experiments showed it to undergo a consistent and significant increase during active hyperventilation with no appreciable change during the passive process (Tables III and IV). This is a concrete example of the untrustworthiness of the cerebral arteriovenous oxygen difference as a criterion of the behavior of either cerebral metabolism or cerebral blood flow, as pointed out in an earlier publication (18).

be capable of leading to a diminution in mean cortical pO₂ sufficient to constitute a major factor in the concurrent deterioration of cortical functions. If one assumes that the relation of cerebral venous pO₂ to mean cortical pO₂ remains unchanged during hyperventilation, one can estimate the diminution in the latter from the observed decrease in the former. The observed mean changes in cerebral venous O₂ content (Table I) were from 11.7 to 8.1 volumes per cent during voluntary and from 10.8 to 7.3 volumes per cent during passive hyperventilation-decreases of 31 and 32 per cent. The corresponding changes in pO_2 on the nomogram of Peters and Van Slyke (14) are from 35 to 22 and from 33 to 19 mm. Hg respectively—decreases of 37 and 42 per cent.

We have as yet no direct information concerning the relation of cerebral venous pO_2 to cortical pO₂ in man. According to recent studies made with an oxygen electrode applied to the exposed brain of the cat, cortical pO₂ varies over a wide range, depending both on the proximity of the electrode to a blood vessel (16) and the state of functional activity of the underlying tissue (17), but there was a clear tendency for the pO_2 in the cortex to be lower than that in the cerebral veins (16). If a similar relation existed in our subjects, the observed decreases in cerebral venous pO_2 would signify that cortical pO_2 had fallen to an even lower level and signs of anoxia would not be surprising. As a matter of fact, our figures both for mean cerebral venous O₂ content during hyperventilation (7.7 volumes per cent) and its decrease below the control level (32 per cent) are practically identical with the corresponding values (7.9 and 32 volumes per cent respectively) reported (7) from experiments on subjects inhaling mixtures having an O₂ content of only 6 to 8 per cent. The associated cerebral anoxia undoubtedly was less severe in our subjects than in theirs because of the higher level of pO_2 at the arterial end of the capillaries in ours, but the severity of the systemic anoxemia required to elicit such a drop in cerebral venous O2 content at least indicates that this change was not inconsequential. Even though we are unable to estimate the part played by cortical anoxia due to diminution in cerebral blood flow in the deterioration in cerebral functions associated with hyperventilation, it seems proper to point out that a major physiological adjustment is involved in addition to the biochemical changes evident in the blood.

Since the mean blood pressure either was unchanged or rose during hyperventilation (Table II), it is clear that the recorded decreases in cerebral blood flow must have been due to some change localized in the brain, and by far the most likely cause is constriction of cerebral blood vessels. These findings, therefore, lend strong support to the already prevalent belief (7, 8, 10, 20) that the cerebral vessels are specifically regulated by the CO_2 tension to which they are exposed. This attractive and seemingly well-founded conception was recently called into question (10, 18) because the first quantitative measurements of cerebral blood flow ever to be made under conditions approaching the normal (18, 19) indicated that the cerebral circulation as a whole is influenced much more strongly by changes in pO₂ than in pCO₂, and no evidence could be obtained that the response to pCO_2 was marked enough to warrant confidence in a specific regulating function by this agent. The measurements of total cerebral blood flow were made on monkeys, whereas those on which the belief in the specificity of CO₂ was based were semi-quantitative observations on the pial or cortical circulation in cats.

The possibility of a species difference has not yet been evaluated, but the most important question, viz., the behavior of man, is answered unequivocally by our present data: the total cerebral circulation of man resembles the pial or cortical circulation of the cat and not the total cerebral circulation of the monkey in its response to hypo-The possible implications of this surcapnia. prising conclusion will not be discussed further at this time than to point out that the most obvious interpretation—that the intrinsic control by pCO₂ is better developed in the cat than in the monkey -is not necessarily justified. It may be that the effects on the subcortical areas in the monkey are equal but opposite to those in the cortex, and thus the total blood flow does not change while flow in the cortex does. It is possible that the response to pCO₂ is more highly developed and, therefore, more subject to derangement by narcosis and experimental manipulations in the monkey

than in the cat. Comparisons of the adequacy of the methods used in these various studies strongly favor the monkey experiments because in these total cerebral blood flow was actually measured. whereas in the cat experiments, changes in blood flow were inferred either from changes in the caliber of pial blood vessels (20), or from changes in temperature of a special thermocouple inserted in the cortex (21). The limitations of these methods are considered elsewhere (10). The possible influence of anesthesia on the cerebral vasoconstriction associated with acapnia will have to be settled by appropriate studies on man; it is unlikely that corresponding data can be obtained in animals before and after the induction of anesthesia.

Cerebral metabolism. From the cerebral arteriovenous O₂ difference and the volume of cerebral blood flow, the cerebral O_2 uptake can, of course, be computed directly. The values obtained are shown in Table III, and the percentile changes during hyperventilation are given in Table IV. One of the most interesting results of these studies is the difference in this respect between the two types of hyperventilation; though active hyperpnea was associated with a consistent and statistically significant increase in cerebral O₂ uptake, passive hyperventilation of approximately the same degree and in the same subjects was not. Since the indicated increase in cerebral O_2 uptake occurred only when the hypocapnia was induced voluntarily, this cannot have been a simple experimental artifact related to imperfect understanding of the true contours of the arterial and venous N₂O curves, nor can it have been due entirely to an acceleration of cerebral metabolism by alkalosis or by a subnarcotic concentration of N_2O . The most probable cause appears to be an actual increase in cerebral O2 uptake associated with the voluntary hyperpnea. If the relatively mild cortical activity, involved in maintaining an arbitrary respiratory cycle in accordance with a signal bell ringing every 10 seconds, is sufficient to produce a measurable increase in the total amount of O₂ used by the brain, a high degree of lability in this function is indicated. If the cerebral arteriovenous O₂ difference during passive hyperventilation can change so as to counterbalance precisely the associated decrease in blood flow, the delicacy with which these two factors are adjusted in relation to cerebral metabolism (18) becomes evident.

The absence of significant decrease in cerebral O_2 consumption associated with a mild diminution in cerebral blood flow in these experiments places them in the same category with the first effects of mild hemorrhage in anesthetized monkeys (18). In both cases, the decrease in volume flow of blood was fully compensated by an increase in the arteriovenous O2 difference, and the total amount of O_2 taken up by the brain did not fall. In the monkeys, there were no signs of cerebral deterioration at this time, but the criteria (wink reflex, unimpaired respiratory activity) were relatively crude, and the presence of anesthesia would already have brought about the counterpart of the more subtle derangements of which signs were evident in our human subjects. When the cerebral ischemia became too marked to be compensated by increasing the arteriovenous O2 difference, marked deterioration of cerebral and medullary functions rapidly ensued in monkeys (18), but we have not made any comparable experiments on man.

The coincidence of mild impairment of cerebral functions with undiminished or actually increased cerebral O₂ consumption may be accounted for in several ways. It is possible that the metabolism associated with consciousness constitutes a relatively small fraction of the total cerebral O₂ uptake, and its behavior is obscured therefore by that of the great mass of brain tissue. This interpretation is not in accord with our finding of a significant increase in total cerebral O₂ uptake during voluntary hyperventilation. A more probable explanation is that the average pO_2 to which the cortical cells were subjected was significantly diminished during hyperventilation, since the cerebral venous pO_2 then was 37 to 42 per cent lower than before (p. 114), and the arterial pO_{1} was not appreciably increased. Even though the product of the decreased blood flow by the increased arteriovenous O₂ difference indicated no change, or even an increase, this in itself means that the venous blood leaving the brain had to be considerably lower in O₂ content and tension than before. A corresponding change in pO₂ within the actively metabolizing cells of the cortex seems reasonable to assume. Finally, it is possible that the cortical and subcortical areas behave differently, perhaps oppositely. Our method is incapable of detecting any but the total change in blood flow or in O_2 uptake in the brain, and there seems no point in further speculation along these lines at present.

It is interesting to note (Table IV) that the fall in pCO_2 in cerebral venous blood during hyperventilation was considerably less than that in arterial. This is undoubtedly a reflection of the concomitant diminution in blood flow, which tends to conserve the CO_2 produced by cerebral metabolism and thus partially to compensate for the profound arterial hypocapnia (26).

Cardiac output. It is seen in Tables II and IV that cardiac output per minute was not significantly changed during voluntary hyperpnea but showed a consistent fall averaging 11 per cent during passive hyperventilation. In each type of hyperventilation, stroke volume was the function primarily depressed, the heart rate increasing in both, but, in the case of the active process, to a degree sufficient to keep the minute volume from falling. The decrease in cardiac minute volume during passive hyperventilation is statistically significant. Examination of the ballistocardiograms discloses the fact that the decrease in stroke volume occurs during the inspiratory phase when the thorax is being expanded by a positive intrapulmonary pressure. This would be expected to cause a sharp decrease in venous return to the right side of the heart which would shortly be reflected in a decrease in left ventricular output. The fact that in period IV (Table II), immediately after the cessation of overbreathing, the outputs per beat and per minute both tend to revert nearly to the control value is evidence that the changes in cardiac output are the result of the mechanical factors associated with the hyperventilation rather than the chemical alterations in the blood; the latter would not change appreciably in so short a time after the cessation of overbreathing.

These results are at variance with the striking increase in cardiac output during active hyperventilation found with the acetylene method (22). They confirm recent studies (23) made by the direct Fick method in which cardiac output was found to fall about 13 per cent during passive hyperventilation of the type used here. The two types of hyperventilation employed in these experiments could have different effects on cardiac output for two reasons: the active type entails voluntary muscular exertion that is lacking in the passive one, while the latter contains a positive intrapulmonary pressure factor that is lacking in the former. Evaluation of these influences is beyond the scope of the present investigation. Other effects on the ballistocardiogram of changing intrathoracic pressures are the subject of a separate report (24).

Blood pressure. Both the mean and the auscultatory values (Tables II and IV) showed a moderate but not statistically significant rise during either type of hyperventilation. In no case was there a fall comparable with that observed in anesthetized animals (3) and humans (4). This discrepancy is probably due to a depression by the narcotic drug of the reactivity of cerebral blood vessels to the constrictor influence of acapnia. The brain cells then suffer a drop in pCO₂ when acapnia is produced because the diffusion gradient for CO₂ is increased, and there is no effective compensation by restriction of the volume of blood irrigating them.

Magnitude of cerebral blood flow and metabolism. Since our calculations of cerebral blood flow are based on the percentage content of N₂O in the arterial and cerebral venous blood and the solubility coefficient of the gas in the brain, they yield a figure for blood flow per unit weight and are reported in terms of 100 grams of brain. A reasonable approximation to the total values can be obtained by adopting an acceptable average figure for brain weight in normal adult males, and a calculation of this type employing the factor 1400 grams is shown in Table V. These figures represent the means of the two series of control estimations (Table III), and they pertain solely to the then existing state of physical and mental inactivity in the recumbent position.

It is interesting to note that according to these calculations about one-fifth of the total cardiac output and about one-quarter of the total O_2 consumption were required to satisfy the needs of the brains of these subjects under these circumstances. Their average weight was approximately 70 kgm., and, therefore, the estimated brain weight repre-

TABLE V

Total cerebral blood flow and cerebral oxygen consumption (assuming a brain weight of 1400 grams) and their respective fractions of cardiac output and total oxygen consumption

	Cerebra	al blood ow	Cerebral consur	l oxygen nption
Subject		Fraction of cardiac output		Fraction of total O ₂ uptake by body
•	ml. per minute	per cent	ml. per minute	per cent
S. H.	826	20.2	55	20.1
L. E.	925	18.2	64	24.0
М. Н.	896	20.4	60	21.6
D. M.	1050	21.4	69	29.8
W. H.	938	20.0	62	24.4
Mean	927	20.0	62	24.0

The figures used for these calculations are the averages of the two resting (control) values in each subject.

sents 2 per cent of the total. These figures speak for themselves as far as the magnitudes of cerebral blood flow and metabolism relative to the rest of the body are concerned. The changes which they would undergo under conditions of altered cerebral, muscular, and visceral activity and under the influence of drugs and other agencies are at present matters for conjecture, as are also the variations to be expected between the sexes, at different ages, and under the influence of various pathological processes involving the brain, the cardiovascular system, the metabolism, and the blood. Our findings in monkeys (18) indicated that the "physiological" range for cerebral O2 uptake (*i.e.*, the range of variation that could be undergone without engendering irreversible or slowly reversible changes in cerebral functional activity) was from about half to nearly double the resting "normal." No comparable values for man are at present available, and even those for the monkey are subject to the restrictions imposed by the experimental procedures (anesthesia, extensive operation, systemic anticoagulants and diversion of the cerebral arterial stream into a system of glass and rubber tubing). Any of these is a potential source of reduction in cerebral blood flow and metabolism, and the effectiveness of the anesthetics in this regard was clearly demonstrated (18).

For these reasons, we suggested (18) that the highest "normal" values in the monkey were probably the proper ones to use as the basis for expectations in intact man. These values in monkeys were, for cerebral blood flow and O₂ consumption, 74 and 4.5 ml. per 100 grams per minute, which would amount to 1040 and 63 ml. per minute in a 1400-gram brain. The corresponding normal resting values obtained in the present experiments on men were 59 to 75 (mean 66) and 3.9 to 4.9 (mean 4.4) ml. per 100 grams per minute; the means for a 1400 gram brain would be 927 and 62 ml. per minute (Table V). Since the monkey experiments involved no assumptions as to the measurement of cerebral blood flow, the fact that even one of them yielded results that were as high as those obtained by a less direct method in intact men indicates that our present estimates in man probably are not excessive. It also confirms the validity of the inferences drawn from the monkey experiments.

As far as we are aware, the figures in Table V are the first of the kind to become available. They are presented as a first step toward the establishment of a new set of normals, but they are also an example of the possibilities with respect to clinical medicine of some of the methods that have been employed in recent researches related to the war effort. It is to be hoped that the collaboration among various types of laboratory workers and clinicians which has made possible the development, and utilization for specific military problems, of new technics for the quantitative measurement of various functions in normal young men, will be continued after the incentive and financial support related to the war have ceased to operate. In the opinion of the authors, one of the greatest possibilities for securing an advantage to human welfare out of the wastage of the present war lies here, for in the past advances in clinical medicine have invariably followed the introduction of new methods, and the number of these developed during the past few years is without precedent.

SUMMARY AND CONCLUSIONS

1. Hyperventilation of moderate intensity was produced either voluntarily or passively in 5 normal young men lying recumbent at sea level. The effects on the following functions were studied: cerebral blood flow (by the N₂O method (11)), cerebral arteriovenous O₂ difference, cerebral O₂ consumption, cardiac output (by the ballistocardiograph (12)), arterial blood pressure, pulse rate, pulmonary ventilation, and total O₂ consumption.

2. Cerebral blood flow invariably diminished, the mean decreases during active and passive hyperventilation being 33 (range 12 to 44) and 35 (range 29 to 51) per cent of the control value. Cardiac output was reduced significantly (2 to 19, average 11 per cent) during passive hyperventilation, but during the active process it was maintained by a concomitant tachycardia. Blood pressure did not fall in any case and tended to rise in most, though not significantly. The cerebral arteriovenous O2 difference invariably increased (41 to 84, average 58 per cent). Cerebral O₂ consumption showed a consistent and significant increase during active hyperventilation (5 to 35, average 15 per cent), no change during passive. Definite signs of impairment of cerebral functions were observed in 5 instances, of tetany in 3.

3. These findings support the belief that cerebral vasoconstriction is one of the important results of hyperventilation, carried out voluntarily or passively with 21 per cent O_2 in normal young men lying at rest at sea level.

4. The increase in cerebral O_2 consumption during active hyperventilation is attributed to an actual increase in cerebral metabolic activity, since no corresponding change was associated with passive hyperventilation to the same extent.

5. The mean findings for cerebral blood flow and O₂ consumption at rest, recalculated on a basis of a 1400-gram brain, came to 927 and 62 ml. per minute, which are practically identical with the highest "normal" values (1040 and 63 ml.) calculated from direct measurements in monkeys (18). This indicates that the present estimates probably are not excessive. According to these mean values, about 20 per cent of the total cardiac output and about 24 per cent of the total O₂ consumption are dedicated to the requirements of the brain (about 2 per cent of the body weight) in normal young men at physical and mental rest at sea level. The mean Q_{0_2} for the normal resting human brain in these subjects was 13.2 (range 11.7 to 14.7).

The collaboration of Dr. Isaac Starr in conjunction with the use of the ballistocardiograph and the interpretation of the records is gratefully acknowledged, as is that of Dr. C. K. Friedland in the performance of some of the experiments. The seven conscientious objectors used as subjects in the present study proved to be willing, cooperative, highly motivated, and unusually intelligent, and we are glad to record our appreciation of their superlative qualities for such purposes.

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HYPOTHERMIA

ITS POSSIBLE ROLE IN CARDIAC SURGERY: AN INVESTIGATION OF FACTORS GOVERNING SURVIVAL IN DOGS AT LOW BODY TEMPERATURES*

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THE USE OF HYPOTHERMIA as a form of anesthetic could conceivably extend the scope of surgery in many new directions. A state in which the body temperature is lowered and the oxygen requirements of tissues are reduced to a small fraction of normal would allow exclusion of organs from the circulation for prolonged periods. Such a technic might permit surgeons to operate upon the "bloodless heart" without recourse to extra corporal pumps, and perhaps allow transplantation of organs.

At the present time, pericardectomy as well as operations designed to revascularize^{1, 2, 3} or repair⁴ the myocardium are in the process of development; these involve the heart wall. Most so-called heart operations, however, are restricted to the anastomosis of vessels about the heart, the most notable in this category being the current operations for congenital heart disease^{5, 6} and a shunt⁷ for mitral stenosis. Intracardiac procedures upon human beings are heroic technics designed to open a stenosed mitral valve and close¹¹ or produce¹² a septal defect in an intact heart with little or no visual control. All these procedures represent advances in our knowledge, but the human heart until now has resisted serious inroads by the surgeon. The shunt operations produce a secondary, although less serious, defect and intracardiac operations under direct vision are still not possible.

A bloodless heart excluded from the circulation is necessary before much further progress can be made in the field of cardiac surgery. Methods to short circuit the heart by an extra corporal heart-lung pump have been under experimental study in different centers¹³⁻¹⁶ for several years. We have used

^{*} Financed in part by a Defence Board of Canada grant. Submitted for publication November, 1949.

hypothermia on the theory that it might prove a simple procedure allowing operations on a diseased or abnormal heart where cannulae in great vessels may be poorly tolerated. A few published reports have been encouraging as to the practical future of this study. Body temperatures as low as 25° C in human beings have been recorded¹⁷ with survival. Temple Fay¹⁸ was able to maintain the body temperature of patients under treatment for cancer at 31° C for several days.

In order to test this hypothesis, generalized hypothermia has been studied by the authors* for two years. One hundred and twenty dogs have been cooled and re-warmed. The steady fall in oxygen consumption produced by lowering body temperature has already been reported.¹⁹ The present investigation of the circulatory changes and cause of death was carried out to make possible cooling to lower temperature levels. The technic of cooling and re-warming has been developed far enough to permit the exclusion of the heart from the circulation by clamping off the vena cavae, with ultimate survival, for much longer periods than has been possible at normal body temperatures.²⁰ During the clamp off the heart has been opened then re-sutured. A report of these experiments will be published in the near future. This procedure is not yet ready for clinical trial, but it appeared worthwhile to report to others interested in this field the difficulties that have been encountered and problems that remain to be solved.

Warm blooded animals at rest have a relatively constant body temperature and display only minor variations in their cardiovascular state. When their body temperature is lowered, however, dramatic changes are observed.

Mature non-hibernating mammals such as the dog will survive cooling under certain conditions down to about 20°C. Differences of opinion exist in the literature as to the cause of death. It appears controversial whether death is due to circulatory or respiratory failure. Artificial respiration and light anesthesia were used in the experiments to be described, making it possible to study what appeared to be a cardiovascular death at temperature usually below 20°C. Interest in such an investigation is stimulated by the knowledge that hibernating mammals with similar normal anatomy can survive temperatures of 3°C.²¹ and, unlike dogs, experience little or no shivering during cooling.

METHODS

Mongrel dogs of medium size, after fasting for 20 hours, were close clipped and cooled by either of two methods. In the early experiments animals were placed in a controlled temperature room at an arbitrary temperature level of six to 12° C. Later, blankets[†] were used through which an alcohol solution at 1° C was circulated in coiled rubber tubing. Both methods produced a similar rate of cooling.

Barbiturates, ethyl ether and vinyl ether have been used as anesthetics to * As well as by R. C. Harrison, M.D., and R. A. Gordon, M.D., University of Toronto.

† Refrigeration unit supplied by Therm-O-rite Products Corp., Buffalo, N. Y.

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determine their relative effects on the cardiovascular system. In each case the smallest amount of the anesthetic agent required to control shivering was employed.

The animals were revived by submerging them to the neck in a hot water bath at 40° to 42° C.

The pulse rate was counted intermittently from the continuous visual electrocardiograph image,* or was obtained by measurement from the electrocardiograph photographic tracings, taken periodically.

Mean arterial pressures were read intermittently from a mercury manometer connected to an arterial catheter which had been inserted through the femoral artery into the aorta.

Mean venous pressures were obtained from a saline manometer connected to a catheter, which had been passed down the right, or occasionally the left, external jugular vein into the superior vena cava. During cooling, zero point of the manometer was set at the level of the dog's midsternum, the dog lying on its side. During re-warming in a water bath the manometer zero point was set on a level with the suprasternal notch. The lowest point of the venous pulse wave was recorded periodically. Either the manometer system or the animals were heparinized.

Cardiac outputs were calculated by the direct Fick principle.²² Oxygen consumption was measured by a 1 liter modified Tissot spirometer connected through a carbon dioxide absorber to an airtight endotracheal catheter. Samples of arterial blood were taken from the abdominal aortic catheter simultaneously with venous blood samples from the right auricle. The position of catheter was checked radiologically. The blood was collected under oil and analyses were carried out on the manometric Van Slyke apparatus.²³

During the process of cooling and rewarming, continuous visual observations and periodic photographic recordings were made on a cathode ray electrocardiograph. Leads I, II and III of the electrocardiograph were connected to German silver needle electrodes which were placed sub-cutaneously on the proper limbs. Arterial blood samples for the determination of serum calcium and potassium were obtained in an oiled syringe through a large bore cannula lying in the aorta. They were centrifuged in a waxed tube. As soon as the clot formed the serum was removed as rapidly as possible. Calcium was determined by the method of Collip and Clark as modified by Fiske and again by C. E. Downs.²⁴ Potassium was determined as by Consolazio and Talbott.²⁵

When respirations failed at lower temperatures positive pressure artificial respiration was used. The lungs were inflated with a 5 per cent carbon dioxide in 95 per cent oxygen mixture ten times a minute.

OBSERVATIONS

The general picture of a dog undergoing cooling and re-warming, together

^{* &}quot;Cathode Ray Electrocardiograph"; supplied by Smith and Stone, Georgetown, Ontario.

with the methods of maintaining arterial oxygen saturation have been described in a previous publication. With proper control of shivering, each dog showed a progressive fall in body temperature and respiratory rate. When the rectal temperature had fallen to 28° C "cold narcosis" supervened, anesthetic agent was no longer necessary to maintain relaxation, and a little later spontaneous respirations ceased. In this state the animals were ideally suite for surgical procedures. The rate of re-warming was faster than the rate of cooling, and spontaneous respirations reappeared at 22° to 27° C. These animals, after seven hours of unconsciousness, were usually up and active two to eight hours



FIGS. I. and 2.—Observations made while cooling a dog to 20° C with re-warming in a water bath at 40° C.

after resuming normal body temperature. Absence of ill effects on examination up to seven months after cooling has been reported.¹⁹ Repeated cooling did not appear harmful.

No attempt has been made to obtain a survival rate in a large group of dogs cooled to a given temperature level such as 20°C with immediate re-warming. In many experiments cooling was continued to the lowest possible limit in order to determine the lethal temperature level. We feel, however, that cooling dogs to 20° with re-warming is a safe procedure.

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Three separate series of animals were studied under different forms of anesthesia. The largest and most complete studies were made on animals under barbiturates. This report is based largely on this series.

HEART RATE

The heart rate was observed in 72 dogs during cooling to levels usually between 18° to 22°C. The 59 dogs under barbiturate anesthesia are reported in this section. All animals showed a decrease in rate from a normal of 120 to 180 per minute as their body temperature fell, agreeing with other observers,²⁶⁻³² and observers not herein cited. An initial transient rise of ten to

15 points in heart rate on first exposure to cold, reported by many of these workers, was observed in the majority of animals; its appearance was noted in those which were more lightly anesthetized. This initial rise was eliminated by deeper anesthesia, under which conditions a steady fall in rate was observed.

Although for each animal a linear relationship was found during cooling between the curves of body temperature and of heart rate there was some variation in the slopes of the heart rate curves because of the initial differences in the normal rates of these dogs. The final rate of temperatures between 18° and 20°C was fairly uniform, the range for the whole group being from 15 to 30 beats per minute (see Figures 1, 2 and 3).

During re-warming there was a rapid increase in heart rate immediately after immersion in the water bath at 40°C. From this point the



FIG. 3.—Observations made while cooling a dog to 20° C with re-warming in a water bath at 40° C.

rate rose with increasing body temperature, parallel to the fall during cooling, although at a given temperature the re-warming heart rate was usually faster. Failure of the heart rate to increase on re-warming was an indication of a reduction in the animal's chances of late survival. A similar variation in the slopes of the re-warming graphs to that noted in cooling was observed.

ARTERIAL PRESSURE

Mean arterial pressures have been studied on 18 dogs during cooling. Six experiments under barbiturate with three of these during re-warming are reported. Cooling in dogs has been shown by Prec *et al.*³¹ to lower blood pressure, but in a relatively constant manner. In our animals, cooling lowered the blood pressure, but in a variable manner.

In four of the dogs a rise in pressure occurred shortly after being placed in the cold environment, a finding in agreement with other observers.^{26, 28-31, 33} Readings are not available on the other two dogs for the first few minutes of cooling; they may or may not have shown initial rises. The early arterial pressure rise was followed by a fall before the animal had cooled more than 2° C. The pressure tended to become stabilized or to rise slightly again, between 32° and 24° C, in all dogs. This trend has not been remarked upon by other workers. Following this short period of stabilization the blood pressure fell off rather sharply, usually in the temperature zone of 24° to 20° C. A mean blood pressure of 16 to 46 mm Hg. was recorded for all six dogs at 20° C. The pressure never fell to zero unless the heart became irregular or stopped (see Figures 1, 2, 3).

VENOUS PRESSURE

Venous pressures have been studied in 27 dogs during cooling and re-warming. Twelve experiments under barbiturate are reported in this section. This study was prompted by the observation in early experiments that in some of the dogs undergoing cooling in the lower temperature a marked dilatation of their superficial veins became apparent. This observation has been made on animals by several authors. Alexander³⁴ reports similar observations having been made on human beings by German investigators in Nazi prison camps.

The pressures in the superior vena cava or the right auricle before cooling were -1.5 to +2.2 cm. of water. There was a fall of one to three cm. in the venous pressure of two thirds of the animals shortly after being placed in the cold blankets. During further cooling there was no consistent or significant change in pressure while good spontaneous respirations were maintained. Usually positive pressure artificial respiration was started at about 27°C. This was followed by an immediate rise of I to 3.5 cm. in venous pressure. From that point until 18° to 22°C, when re-warming was started, there was a further gradual rise in pressure. Pressures up to 20 cm. of water have been recorded.

As a rule venous pressures over 6 cm. of water maintained for any length of time were followed by abnormal heart action, from which the dogs seldom recovered in the earlier experiments. There were no records of a negative verous pressure at a body temperature below 22°C.

During resuscitation there was a further rise in venous pressure shortly after immersion in the water bath $(40 \,^{\circ}\text{C})$, sometimes followed by ventricular fibrillation and death. If the animal experienced the sudden increase in heart rate usually following immersion in warm water, the pressure rise was only temporary, and soon fell to within normal limits. A further fall in pressure to a negative range occurred with the onset of spontaneous respirations.

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It was apparent that a full understanding of venous pressure changes might well hold the key to a more exact knowledge of cardiovascular failure associated with hypothermia. With this in mind an appraisal of factors affecting venous pressure changes was made.

There were occasional transient periods of shivering during cooling in a few animals in this series. Moderate to severe shivering was associated with an increase in venous pressure, but the pressure returned to normal when the shivering was controlled by further anesthetic. Crismon, who did not control shivering in rats, reported a consistent and marked rise in venous pressure during cooling which eventually decreased with cessation of shivering.

There were no records of negative venous pressure after the animal had been on positive pressure artificial respiration for any length of time. In two young dogs in which spontaneous respirations were maintained to 22°C and 24°C a corresponding delay in rise of venous pressure occurred.

As a general rule the greater the depression of heart rate, the greater was the tendency to develop increasing venous pressure as cooling proceeded.

VENESECTION

It has been observed incidentally that drawing off blood samples at very low temperatures increased the heart rate. With the observed correlation between a rising venous pressure and the onset of ventricular fibrillation, the obvious procedure to investigate was the effect of venesection.

Previous to this, 17 experiments had been terminated prematurely by a "cardiac crisis" with the sudden onset of ventricular fibrillation in 15 and cardiac arrest in two as observed in the continuous electrocardiographic image. Fifteen of the 17 animals died without resuming normal heart action (including the two with cardiac arrest). This was so in spite of immediate immersion of most of the animals in the water bath within one to two minutes of the development of fibrillation.

Venesection has been performed 60 times. The first experiment was dramatic in its result. At 19°C and with a venous pressure of 7.5 cm. of water, ventricular fibrillation appeared and the dog was immediately placed in the warm bath. Four minutes later, on removing 30 cc. of blood from the jugular vein, a run of normal beats was produced. Removal of a further 100 cc. established normal heart action and the dog survived. Venesection was successful in 20 out of 28 instances in which it was used in an attempt to restore normal heart action after "cardiac crisis" in dogs cooled below 21°C. This sequence of events has occurred two or three times in the same experiment during cooling and re-warming with survival of the animal. On six occasions the measure had no effect and twice it converted ventricular fibrillation into complete A-V block with independent action of auricles and ventricles. Amounts withdrawn varied between 30 and 150 cc. and averaged 80 cc.

The procedure was used 32 times as a means of reducing a venous pressure which had become dangerously high. By an average withdrawal of 80 cc. the pressure was reduced an average of 2.0 cm. water. On one occasion no fall in venous pressure followed venesection.

In three experiments an attempt was made to keep the venous pressure normal during cooling by repeated small venesections of 50 cc. of blood as required. After each withdrawal the venous pressure was lowered, the heart rate increased and ST interval in the electrocardiogram shortened. The animals were cooled to lower levels than that usually attained, but in each case two thirds to three fourths of their total blood volume was eventually removed with final "cardiac crisis" and death.

CARDIAC OUTPUT AND PERIPHERAL RESISTANCE

The cardiac output was measured at intervals during cooling and re-warming in seven dogs making use of the Fick principle.²² The results in three dogs are shown in Figures 1, 2 and 3. A gradual fall during cooling and a rise during re-warming is evident with a cardiac output averaging 18.1 ml./Kg./

Experiment	Rectal	Index
Number	Temperature	Periph. Resistance
93	38.0	9
	27.3	20
	20.0	12
	31.7	20
	38.0	16
90	37.2	9
	27.2	40
	20.3	20
	30.0	7
	37.2	6
89	36.1	7
	24.4	12
	20	15
	31.1	9
	38	13

min. at 20°C. This represented a fall to 14 per cent of the average of the pre-cooling figures.

Final re-warming values were below the pre-cooling in all but one. In this experiment the observations are made one hour after normal body temperature had been reached and the animal had been removed from the warm bath.

Peripheral resistance was assessed by applying the formula R = P/F (peripheral resistance = blood pressure/cardiac output). Without discussing the reliability of this formula the results are given in Table I. These calculations are from the experiments represented in Figures 1, 2 and 3.

The marked rise in the index of peripheral resistance is evident in each of the three dogs examined.

THE PERIPHERAL VASCULAR BED

As cooling progresses the peripheral vessels undergo a gradually increasing vasoconstriction. No attempt has been made to measure the degree or rate of this process, but the femoral and subclavian artery and vein have been

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exposed on numerous occasions and at various temperature levels. At 20°C. it is practically impossible to do a venous or arterial puncture through the skin, and on exposure the vessels appear constricted to less than one-half diameter, although blood flow continues.

Microscopic examination of the conjunctival vessels before and during cooling (using a technic previously described³⁵) revealed the development of marked "vascular stasis" in the lower temperature ranges, with complete



FIG. 4.—A group of representative electrocardiograms at low temperature. — (I, 2 and 3) The changes in the electrocardiogram on cooling and re-warming. The standardization in (2) and (3) is half that in (I) since it was impossible to photograph the whole complex with normal standardization at low temperature. (4) Ventricular fibrillation in a dog at low temperature. (5) Slow sinus rhythm with a ventricular premature beat. (6) Slow A-V nodal rhythm at 15° C. Interval between beats 8 to 12 seconds. (7) The same at 14°C. Intervals between beats is about 14 seconds.

cessation of flow in some arterioles and in veins as large as 60 microns in diameter. This effect was considered due to obstruction to flow caused by the "intravascular agglutination of erythrocytes" (sludged blood) along with vasospasm.

CHANGES IN THE ELECTROCARDIOGRAM WITH COOLING

Representative electrocardiograms in cooled dogs are shown in Figure 4. The continuous electrocardiographic image has been followed during cooling
and re-warming in 95 animals. Tracings at various temperature levels have been taken and studied on 15 representative experiments. During cooling the rate slows, sinus rhythms with rates of 15 to 30 per minute being usual at 20°C. The PR interval is roughly twice the PR interval at 37°. The duration of the QRS becomes difficult to define at temperatures below about 25°C. The initial rapid deflections are succeeded by a long wavy electrical disturbance. The initial rapid deflections are called the QRS, even though it is sometimes hard to decide whether part of the subsequent disturbance rightly belongs to the QRS. The subsequent electrical disturbance, which lasts until the diastolic isoelectric line is reached, is considered to be the T wave. Around 20°C it is nearly always a negative wave. It may become negative at any stage of cooling, and the earlier it appears the poorer the prognosis. The duration of the QRS is usually about doubled, and the QT interval (electrical systole) is three to four times as long as at 37 degrees. This can be seen by a glance



FIG. 5.—The changes in certain of the electrocardiographic measurements with cooling and re-warming in a representative dog. Dotted line is re-warming.

at Table II.

The voltage of the QRS is difficult to measure in the dog, since the deflection is often so great and rapid that it does not photograph, even though it may be visible on the cathode ray screen. It can be photographed by lowering the sensitivity of the instrument. About 24°C the voltage may fluctuate, more often it increases. Below 24° the voltage usually falls, but this is not constant; it was observed in five out of seven dogs in which it was possible to measure the QRS voltage in our records. Figure 5 shows that the PR and QT distance increases much more rapidly with falling body temperature, once 30°C is passed. If cooling is continued the rhythm changes at some point, usually below 20°C and above 16°C. The type

of change is variable. The most common sequence of events is the appearance of ventricular ectopic beats followed by ventricular fibrillation and death. There

TABLE II.—Changes in the Electron	cardiogram at Low Ba	dy Temperature (Nine dogs).
Rectal Temp. °C.	36.8°C (32° to 39°) (before cooling)	19.3°C (18.7° to 20°C)
Heart rate PR interval QRS duration QT interval	143 (100 to 200) per min. 0.10 (0.07 to 0.12) sec. 0.05 (0.04 to 0.06) sec. 0.25 (0.18 to 0.36) sec.	25 (20 to 30) per min. 0.22 (0.16 to 0.28) sec. 0.09 (0.07 to 0.12) sec. 1.04 (0.92 to 1.14) sec.

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is usually little warning. With vigorous ventricular fibrillation it is impossible to identify P waves. Direct observation of the heart, however, discloses that there is a continuance of regular auricular beats for periods up to 20 minutes after onset of ventricular fibrillation. These become irregular and eventually both auricle and ventricle come to cardiac arrest in diastole.

On rare occasions, and usually below temperature levels of 17°C, instead of ventricular fibrillation, a pacemaker in or below the AV node has taken over, resulting in the electrocardiographic appearance of nodal rhythm, or of slow idioventricular rhythm. The interval between beats may be as long as 17 seconds, with absence of P waves.

Survival after ventricular fibrillation has been described under the section on venesection.

If the animal is re-warmed, the changes in the electrocardiogram revert toward normal (Figure 5). However, even though the heart rate, the PR interval, the duration of the QRS complex and the QT interval return to normal, the voltage of the QRS is often lower than before cooling, and the T waves and the ST segments may be of a different form. Records taken on a series of six animals one to three months after cooling showed normal tracings. These changes in the electrocardiogram with cold are not unlike those reported by other observers.²⁸⁻³¹

DIRECT INSPECTION OF THE HEART AND CARDIAC RESUSCITATION AT LOW BODY TEMPERATURES

Thoracotomy has been performed upon 20 dogs at low body temperatures ranging from 15°C to 22°C, no anesthetic agent being required. The heart has been observed directly with its normal slow beat and as changes in rhythm occurred. Several methods of cardiac resuscitation have ben employed.

At these temperatures a state of almost pure cold narcosis exists as an anesthetic, two hours having usually elapsed since removal of the anesthetic agent.

Interesting slow heart action was observed. As the venous pressure increased, overfilling and distention of the right auricle was noted during diastole with a slow but powerful contraction occurring only a few times a minute. It is an intriguing sight resembling a slow motion movie recording of heart action. Ventricular fibrillation appeared at low temperatures with little warning and was characterized by a slow irregular writhing of the ventricular musculature. Usually the auricle continued a regular beat following the onset of ventricular fibrillation but, as a rule, for not more than 15 to 20 minutes. Isolated, irregular auricular beats often continued for an hour with a reduction in vigor of the ventricular fibrillation and eventual cardiac arrest in diastole.

Cardiac resuscitation has been employed in the form of: (1) electrical stimulation with a faradic current, (2) mechanical prodding, and (3) manual cardiac massage. Normal beats with auricular and ventricular com-

plexes have been produced by stimulation of the SA node area in the right auricle with the heart in both ventricular fibrillation and following cardiac arrest. Electrical stimulation in such cases was of low voltage from an induction coil. After a period of about 15 minutes only the auricle will respond to this stimulation. Solitary ventricular contractions may sometimes be obtained by similarly stimulating the ventricular muscles for a further period of about 15 minutes. Epinephrine, barium chloride, digitalis and Coramine have all been used as an intracardiac injection without significant response. A strong electric shock was applied to three hearts while in ventricular fibrillation according to the defibrillation technic described by Beck.³⁶ One of these hearts immediately developed cardiac arrest, the others were unaffected.

No cases of ventricular fibrillation or cardiac arrest were permanently revived by these methods alone. Rapid removal of venous blood, which reduced or eliminated the ventricular fibrillation, followed by cardiac massage and re-warming, did allow revival of a few.

TABLE III.—Serum Calcium and Potassium Changes in Hypochermia(Seconal anesthesia).					
Experiment	Serum Calcium Mg. %		Serum Potassium Mg. %		
	Pre-cooling	Hypothermic	Pre-cooling	Hypothermic	
	36-37.5°C.	19.5-21.5°C.	36-37.5°C.	19.5–21.5°C.	
XXVI	. 10.0		12.80		
XXVII	. 12.20		12.80		
XXXII	. 9.96		14.86		
XXXIII	9.94		17.40		
XXVIII	. 11.30		14.43	14.82	
XXI	. 15.02	12.40	10,95	13.30	
XXIX	. 12.0	16.0	10.92	12.87	
xc	. 10,60	11.40	14.46	16,81	
XCIV	. 10,20	11.20	14.14	16,21	

SERUM CALCIUM AND POTASSIUM CHANGES

This investigation was carried out to determine whether there were electrolytic changes which might account for the cardiovascular collapse encountered in cooling at low temperatures.

Using barbiturate anesthesia and methods previously described, estimations were made before cooling and again in the temperature zone of 19° to 21°C. The enclosed table illustrates a constant rise in serum potassium with a variable effect upon serum calcium. This is for the most part similar to the results obtained by Elliott and Crismon,³⁷ who, however, noted a consistent rise in both calcium and potassium level in rats.

EFFECTS OF ANESTHETICS

Two further series of dogs have been studied, using different types of anesthetic agents. Cardiovascular changes observed were compared to the barbiturate series just described.

Series II: Vinyl Ether. This is a very rapidly acting form of inhalation anesthesia. As in the barbiturate series, just sufficient was administered to

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control shivering. The blood pressure, heart rate, respiration, venous pressure and electrocardiogram were recorded on five dogs.

During cooling, their general condition appeared better than the dogs under barbiturate. There was improved heart action, slightly faster heart rate, and better respiration. Spontaneous respiration ceased on an average at 22° C. and reappeared at 23° C. The venous pressures were maintained at a lower level.

It was a surprise to find that only one of the five dogs survived the experiment. This dog died four days later with signs of clinical jaundice and Vandenberg estimation in the blood of 7 units. The other four died during rewarming and all showed congested livers at autopsy.

Series III: Ethyl Ether. Thirteen dogs were studied in this series. The heart rate was followed in all. The venous pressure was recorded in ten, the arterial pressure in four. There was no significant difference in the readings obtained in this group compared with those under barbiturate anesthesia. The heart showed the same tendency to develop abnormal action at low temperature.

DISCUSSION

Most workers have accepted shivering as a part of the physiologic response to cold, observing its variability during the early stages of cooling and its gradual decline as cooling proceeds. They have made their experimental observations in the presence of shivering. In these studies in hypothermia, shivering has been controlled in order to study the pure effects of cold on the organism. This method of approach was used in a previous study of oxygen consumption¹⁹ and the possible source of error introduced by the use of anesthetic was discussed. Admittedly anesthesia affects heart action and the vascular bed to some degree, but when given carefully in regulated doses the resultant absence of shivering allows ready cooling and technically more reliable observations. It is the approach to hypothermia which one would anticipate in its eventual clinical application.

Figures 1, 2 and 3 show a marked fall in cardiac rate, cardiac output and blood pressure (which is remarkable when one realizes that it is compatible with life). The low hydrostatic pressure and vascular stasis from agglutination of erythrocytes must leave the peripheral tissues almost devoid of blood flow. Since skin and muscle temperature are well below the rectal temperature¹⁹ their oxygen requirements are negligible. The whole animal at 20°C uses about 15 per cent of its normal oxygen consumption,¹⁹ which roughly corresponds to the reduction in cardiac output at that temperature level. Recently published experiments¹⁷ report clamping off the heart for periods of nine minutes at normal body temperature. We have excluded the heart from circulation for longer periods with the animal at body temperature of 20° but for the prolonged exclusion considered necessary for human cardiac surgery, lower body temperatures will likely have to be attained. When dogs are cooled with the aid of a light anesthetic to prevent shivering, they become hypoxemic due to respiratory depression. This respiratory depression is a combined result of the anesthetic agent and cold. Artificial respiration below a certain temperature level is necessary to maintain life and it has been used in each experiment recorded. Such an experimental animal will usually survive cooling to about 20°C provided he breathes a mixture of 5 per cent carbon dioxide in oxygen.¹⁹ Below this temperature range he usually develops ventricular fibrillation, which is invariably fatal unless venous section is employed and re-warming instituted.

Under the condition of these experiments death in hypothermia appeared to be the result of sudden cessation of normal heart action (cardiac crisis). The possible causes of this may be summarized as follows:

I. Primary effect of cold on the heart

- A. Inhibition of impulse formation.
- B. Interference with function of conducting tissue.
- C. Failure of myocardium to respond.
- 11. Cardiac crisis secondary to:

A. Overwork from too great a peripheral resistance, caused by intense vasospasm, induced by cold.

B. Overwork caused by overloading, from increased venous return, due to reduction of the vascular bed by vasospasm,

- C. Anoxia of the heart.
- D. Chemical changes in the blood
 - 1. Fluid and electrolyte shifts.
 - 2. Circulating toxin.
- E. Depression of nervous system
 - 1. Central, cardiac center.
 - 2. Peripheral, autonomic nerves.

I A. Direct observation of the persistence of regular auricular beats in the presence of early ventricular fibrillation indicates the continuance of impulse formation and rules out inhibition of impulse formation as cause of death.

I B. There is evidence that in the cold heart the conducting tissues function poorly. Figure 5, showing the relation of PR interval to temperature, shows a very great increase for a small drop in temperature once 20° C is passed. Whether or not this impaired conduction is responsible for the great tendency of the cold ventricle to fibrillate and then stop is not known. The late response of the cardiac muscle to direct stimulation, in our attempts at cardiac resuscitation as described, could be due either to increased myoneural threshold or depression of the conducting mechanism.

I C. The primary effect of cold on the heart may well be a chief cause of death. It has been demonstrated that isolated heart preparations from non-

hibernating animals cease functioning at 16°C while that of a hibernating animal continues to 2° and $3^{\circ}C.^{38}$

II A. The concept of a high peripheral resistance at low body temperatures producing an overworked heart is suggested by our calculation of peripheral resistance (Table I³⁹) and by the intense vasoconstriction present in the extremities. One would expect the "vascular stasis" observed microscopically to cause a great increase in peripheral resistance. Arteriovenous shunts probably open as a compensatory mechanism.³⁵

On examining the blood pressure changes during cooling, one does not see a temporary rise in blood pressure before cardiac failure which might be expected if this concept were true. However, there is a tendency for the blood pressure to remain at a relatively constant level following an initial fall until about 24°C when it usually falls rather more sharply.

II B. It was observed that an increasing or prolonged increase in venous pressure was a forerunner of ventricular fibrillation. Our initial interpretation of this was that it was a result of developing cardiac failure. However, we have recently considered the increased venous pressure as a possible cause of failure. This was first suggested by the favorable effect on heart action produced by venous section as described above. We were able to increase the rate, reduce venous pressure, and bring a heart back from ventricular fibrillation to normal by venous section.

Recent workers^{40, 41} have shown that venesection improves cardiac output while lowering the venous pressure in low-output congestive failure. Their theory that relief from overstretching in diastole allows more efficient ventricular contraction is in keeping with our observations of the effect of venesection in the cold state.

The increased venous pressure may be partly due to the generalized constriction of the vascular bed. It is definitely produced by the institution of positive pressure artificial respiration, which in itself may be a large factor in the cause of death. It was apparent that increased venous return at best is only a contributing factor to cardiac failure. Our experiments in which the venous pressure increase was prevented by repeated venous section only allowed us to cool the dogs a few degrees further.

II C. The cardiac failure in hypothermia is similar to that induced by hypoxemia, both in its course and in the electrocardiographic changes observed. One likely cause for this in the presence of full oxygen content of arterial blood would be reduced coronary flow occasioned by the low systemic blood pressure. Perhaps reduction in the availability of oxygen, caused by low body temperature,¹⁹ is sufficient to produce serious myocardial anoxia.

II D. Biochemical changes in the blood induced by cold are being studied and will be fully published later. The potassium and calcium changes may be significant factors in the mechanism of cardiac failure.

Workers who have studied the cardiac effects of changes in blood level of calcium and potassium have dealt with much greater variations than were observed in this study. It is difficult to conceive of the change noted in these experiments being the sole cause of the dramatic electrocardiographic changes seen, although Elliott and Crismon³⁷ conclude that there is an increased sensitivity to injected potassium at low body temperatures. The statistically significant figures of these workers for potassium elevation were produced under different conditions. The rats of their experiment were shivering violently and perhaps liberating potassium from the liver.

Circulating toxin from the liver or accumulated as a result of the reduced renal output could be a factor.

II E. The mode of death does not suggest a central depression of the nervous system, although denervated heart preparations have not been studied. Chatfield⁴² has recently demonstrated that the peripheral nerves of a hibernating golden hamster did not cease functioning until an average temperature of 3° to 4° C was reached, while nerves from (non-hibernating) rats ceased functioning at an average temperature of 9° C.

Behind all this discussion of the mechanism of cardiac failure is the basic problem concerning the mode of action of hypothermia. Does cold below 20°C prevent oxygen from entering the tissues? Does it depress some phase of cell metabolism? We feel that the intact dog may never be reduced to the low temperature attained by hibernating animals without recourse to special procedures. The difference may be in the conducting mechanism of his nerves or in the anatomy of the arteriovenous shunts in the peripheral vascular bed. Other factors likely contributing to "cardiac crisis" in dogs at low body temperature are cardiac anoxia, overfilling of the heart, and electrolytic changes in the blood.

SUMMARY

1. Hypothermia was induced in dogs, with shivering controlled by anesthetic, in order to study the physiology of the cardiovascular system and learn something of the mechanism of death at low body temperatures.

2. This was investigated to improve our method of cooling with a view to excluding the heart from the circulation for longer periods.

3. Re-warming was accomplished by means of a water bath at 40°C.

4. There was a gradual fall of blood pressure, heart rate and cardiac output to very low levels as cooling progressed, with a comparable rise on re-warming.

5. Intense vasoconstriction was observed in the gross, and vascular stasis with erythrocyte agglutination observed microscopically at low body temperatures.

6. Venous pressures proved a valuable guide to the condition of the heart. An increase in venous pressure over too long a period was often followed by "cardiac crisis" and it could be temporarily forestalled by venesection.

7. Electrocardiographic studies during cooling and re-warming are summarized.

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8. Ventricular fibrillation usually caused death between 16° and 22°C.

9. Return of the heart from ventricular fibrillation to normal with revival has been accomplished by venesection and immediate re-warming. Cardiac resuscitation was attempted through a thoracotomy incision.

10. A table of the possible causes of death has been drawn up and the various factors discussed.

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