HEAD injuries have presented a problem to physicians since prehistoric times. Most of the important works on surgery, from the first written record, the Edwin Smith papyrus, have contained methods for their treatment. Until the nineteenth century, however, the main emphasis in the treatment of skull fractures was placed on the care of the injured skull and scalp. Hippocrates had proposed prophylactic trepanation, but the rational for this was not clearly expounded, and later surgeons argued its merits. It appears that the principle expressed by Rhazes in about 900 A.D.—that in head injuries compression of the brain is more important than damage to the skull—was overlooked until relatively recent times. In fact, according to Silvester O’Halloran, an Irish surgeon (1728–1807), murder by blows to the head was not usually considered punishable in the British Isles in the eighteenth century unless a skull fracture could be demonstrated.

By the end of the nineteenth century it was recognized that cerebral contusion and edema could cause increased intracranial pressure without coexisting hematomas. Decompressive trephining was proposed by Jaboulay in 1896, and in 1908 Cushing advised subtemporal decompression in such cases. However, as experience accumulated, decompression was performed less often.

Also at the end of the nineteenth century, surgeons began to perform major operations on the brain, and cerebral edema was frequently encountered.

"The relief of increased intracranial pressure during operative procedures was a problem met by various techniques. Ventricular puncture and drainage early used by surgeons was one of the most important aids in operating upon the hypertensive brain. Other less dramatic practices consisted of the use of continuous lumbar puncture drainage or the mere milking of cerebrospinal fluid from the opened arachnoid in the operative wound. The posterior cistern was opened in procedures where lumbar puncture was inadvisable...

Bleeding and purging had been performed in the treatment of craniocephalic injuries for centuries, and during the early development of neurosurgery various indirect methods of reducing intracranial pressure were introduced—repeated lumbar puncture, dehydration, and the administration of hypertonic solutions.

In 1919 the important pioneering work of Weed and McKibben reported the effects of intravenous solutions upon brain bulk and cerebrospinal fluid pressure. In this same year perhaps the earliest account of the clinical use of hypertonic solutions (25 per cent glucose by vein) to decrease brain volume was given by Haden. The oral use of hypertonic salt solutions received brief notice by Cushing and Foley in 1920, and in the same year Sachs and Belcher reported the use of intravenous solutions to control excessive swelling of the brain at the time of craniotomy. Further studies of the use of other salts and solutions followed.

Since that time it has become recognized that the temporary reduction in intracranial pressure by the use of various hypertonic solutions is frequently followed by a later "rebound overshoot" in pressure when the effect of the solution becomes dissipated. However, hypertonic solutions have become widely employed in the treatment of intracranial hypertension, and the search for better agents continues.

References


EXPERIMENTAL ALTERATION OF BRAIN BULK*

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Received for publication March 22, 1919

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 cerebrospinal 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. of 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 formalin. In spite of all the care it was possible to exercise, it was soon 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 occipito-atlantoid 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 gyri 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 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 cerebrospinal 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
PLATE I

Fig. 1. Photograph $\times \frac{3}{4}$. Cat no. 1804. 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)
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 water. 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 fixation. The Prussian blue in almost every case was found to have passed 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 toxicities 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 be-

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 X1. Cat no. 1402. Adult female. Control. Well-nourished, normal animal. Sacrificed with ether. Transverse section through optic chiasma. Fixed by injection with 10 per cent formalin.

Fig. 4. Photograph X1. Cat no. 1309. Young adult female. Occipito-atlantoid 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 X1. Cat no. 1304. Transverse section through optic chiasma of brain shown in figure 1.

Fig. 6. Photograph X1. Cat no. 1371. Transverse section through optic chiasma of brain shown in figure 2.

Fig. 7. Photograph X1. 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 185 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 X1. Cat no. 1364. Young adult female. Occipito-atlantoid 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.
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.
neath 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 disturbance 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 of 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 and dura. The injection of Ringer's solution was from a burette, and 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

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 X\textsuperscript{4}. Cat no. 1506. Adult male. Weight 2,100 grams. Temporal decompression on left side. Intravenous injection of 16\textsuperscript{4} 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 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. 12. Photograph X\textsuperscript{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 begins; 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 X\textsuperscript{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 X\textsuperscript{1}. Cat no. 1505. Adult female. Weight 2,050 grams. Temporal decompression on left side. Intravenous injection of 16\textsuperscript{4} 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 X\textsuperscript{1}. Cat no. 1536. Adult female. Weight 2,490 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 X\textsuperscript{1}. Cat no. 1532. Adult male. Weight 2,350 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 X\textsuperscript{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.
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 2,500 grams. Control intravenous Ringer.

<table>
<thead>
<tr>
<th>Time</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.46 a.m.</td>
<td>Ether with intratracheal tube.</td>
</tr>
<tr>
<td>10.15 a.m.</td>
<td>Double subtemporal decompression. Dura opened. Brain lies with normal convexity, pulsation and circulation good.</td>
</tr>
<tr>
<td>10.20 a.m.</td>
<td>Cannula in vein of fore-leg connected with burette containing Ringer's solution.</td>
</tr>
<tr>
<td>10.25 a.m.</td>
<td>Injection begun. Brain as before.</td>
</tr>
<tr>
<td>10.33 a.m.</td>
<td>25 cc. in. Brain as before.</td>
</tr>
<tr>
<td>10.38 a.m.</td>
<td>50 cc. in. Brain slightly more convex.</td>
</tr>
<tr>
<td>10.43 a.m.</td>
<td>90 cc. in. Brain as before.</td>
</tr>
<tr>
<td>10.50 a.m.</td>
<td>100 cc. in. Brain normally convex, shows no bulging. Pulsation free, circulation good. Injection stopped.</td>
</tr>
<tr>
<td>11.10 a.m.</td>
<td>Brain lies normal as before. Pulsation free.</td>
</tr>
<tr>
<td>11.20 a.m.</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 maximum. The pressure of the brain on the dura at the edges of the 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.

<table>
<thead>
<tr>
<th>Time</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.50 p.m.</td>
<td>Ether with intratracheal tube.</td>
</tr>
<tr>
<td>4.00 p.m.</td>
<td>Double subtemporal decompression.</td>
</tr>
<tr>
<td>4.15 p.m.</td>
<td>Dura opened. Brain lies with normal convexity, pulsating freely. No trauma to brain or membranes.</td>
</tr>
<tr>
<td>4.18 p.m.</td>
<td>Cannula in vein of fore-leg connected with burette containing sterile distilled water.</td>
</tr>
<tr>
<td>4.19 p.m.</td>
<td>Injection begun. Brain bulges immediately after beginning of injection.</td>
</tr>
<tr>
<td>4.25 p.m.</td>
<td>Brain bulges more.</td>
</tr>
<tr>
<td>4.31 p.m.</td>
<td>50 cc. in. Brain bulges markedly with pulsation; circulation good.</td>
</tr>
<tr>
<td>4.33 p.m.</td>
<td>75 cc. in. Brain bulges markedly. Pulsation slight, circulation good.</td>
</tr>
</tbody>
</table>
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. Convulsions 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 13 (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 3 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.

Salt. Intravenous injections of a hypertonic solution (30 per cent 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 sides. The conditions prevailing in these experiments were similar to 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 pulsation. In figure 11 is shown the result of an experiment in which a single opening was made in the skull, and 16½ 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 markedly shrunkened brain.

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 2,250 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. Camula 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 13, 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 herniated 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 younger 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 gyri 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 Formalin-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 sulci laterals 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 salts. All the specimens tended to approach the normal when the 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 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 opened**

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 fluid-coagulum 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 attempted. That there are histological changes in brains relieved by decompression is certain, but these changes need more accurate study and control before any sane effort can be made to explain them accurately. The changes described have no doubt been influenced by the 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 cerebral-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 tre-
phined 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 pressure-change 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 cerebro-spinal 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 conditions. Monro, of course, qualified his theory by consideration of 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, cerebrospinal 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 intravascular 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 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 hypertonic and hypotonic 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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