STUDIES IN EXPERIMENTAL BRAIN SWELLING AND BRAIN COMPRESSION*

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The studies reported herein offer a correlation between water-induced "brain swelling," intracranial pressure and volume, and water and electrolyte content of the brain, and offer observations on experimental cerebral compression.

Brain swelling has been defined variously and often used synonymously with brain edema. While the latter process may or may not be the cause of the swelling, it implies that convincing evidence is available of excessive fluid, primarily interstitial, within the tissues. In the present studies, the criteria for brain swelling are 1) an apparent increase in bulk of the brain and 2) a corresponding rise in cerebrospinal fluid pressure in the absence of obstructive hydrocephalus, tumefaction, or vascular obstruction.

In 1919 Weed and McKibben demonstrated the ability that intravenously administered distilled water has in producing brain swelling in the cat. This work stands as a reference point. The occurrence of associated histologic alterations as seen in the rabbit was noteworthy. Fishman reported rises of cerebrospinal fluid pressure in dogs when 5 per cent dextrose in water was given both with and without the presence of an extradural mass which raised the base-line pressure above normal. Systemic administration of water and techniques of local compression of the brain have been utilized in these studies.

WATER ADMINISTRATION

Adult mongrel cats of either sex were utilized. Under intravenous pentobarbital sodium anesthesia, the animals were placed in a head-fixation apparatus. The cisterna magna was exposed and cannulated, and the calvarium was uncovered. The animals were then heparinized. Continuous records were made of both the femoral arterial pressure and the cisternal cerebrospinal fluid pressure via a Statham transducer on a Sanborn apparatus. In 20 animals, distilled water at 37°C was administered intravenously in a dosage of 40 ml. per kg. at a rate of 60 drops per min.

Ten cats were sacrificed at the completion of the intravenous drip, and 10 were observed for 60 minutes following the conclusion of the water drip.

Pressure Measurements. When water was administered to these 20 animals, the cisternal pressure rose from a mean pre-injection pressure of 83

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mm. H₂O to 293 mm. H₂O. These pressure relationships are summarized in Table 1, from which it can be seen that intravenously administered distilled water produced elevations in the cerebrospinal fluid pressure above those recorded in the control animals, as well as above those in animals receiving physiologic salt solution in the same dosage.

When animals treated with water in a similar fashion were observed with the calvarium removed, the brain appeared to swell into the cranial defect, thus fulfilling our criteria of cerebral swelling.

Volume Measurements. A second series of 10 animals received distilled water intravenously in identical fashion. At the completion of the infusion, the calvarium was removed with a dental saw. The brain was sectioned at the bony tentorium, removed, and weighed. Its volumetric displacement of water was then measured. The calvarium cap was resealed in place, and a small opening into the cap was made to fill the cranium with fluid and measure its capacity. In 9 control animals to which no distilled water had been administered, brain volume was 19.1 ± 2.0 ml. and intracranial volume was 21.0 ± 1.3 ml. In the 10 animals to which water was administered, brain volume averaged 18.7 ± 1.2 ml. and intracranial volume 19.8 ± 1.8 ml.

Percentages of intracranial volumes occupied by the brains in this group of animals to which distilled water had been administered were compared with similar data from the control animals. It was found that among the latter the mean occupancy by the brain of the intracranial space was 90.0 ± 6.8 per cent, and among the former animals the figure was 94.8 ± 4.5 per cent. P > .05. Increase in bulk of the brain would therefore appear more apparent than real.

Artificial Respiration: Venous Pressure and Blood Content. Obstruction to the venous system of the calvarium might raise the cisternal pressure and increase brain bulk, and CO₂ retention caused by inadequate pulmonary ventilation (barbiturate anesthesia) might be another pitfall in the search for the correct explanation of the phenomenon under study. 17, 21, 22
To elucidate the role of such possible variables, groups of 5 to 11 animals each were studied by measuring both cisternal cerebrospinal fluid pressure and venous pressure in the superior longitudinal sinus. (Catheterization of the sinus *per se* did not alter cisternal cerebrospinal fluid pressure or the blood content of the brain.) Such groups of animals were compared with other similar groups in which methods of controlled artificial respiration were utilized (Fig. 1). At the completion of pressure measurements, the brains of all animals were homogenized and measured for hemoglobin content.  

Under the conditions of our experiments, controlled artificial respiration
was associated with no significant alteration in hemoglobin content of the brain.*,10,15,21 Artificial respiration produced a reduction in the cisternal cerebrospinal fluid pressures which was not statistically significant (P > .05). Reduction of venous pressure in the longitudinal sinus during artificial respiration, however, was significant (P < .05). When two additional groups of animals were given distilled water, the application of artificial pulmonary ventilation to one of these again did not significantly alter the cisternal pressures observed between the groups (Fig. 2).

It would appear from the above that venous congestion, inadequate

* 6 animals, no respirator: 0.20 ± 0.04 gm. per cent hemoglobin
8 animals, respirator: 0.17 ± 0.03 gm. per cent hemoglobin

P > .05.
excretion of respiratory CO₂, and increased blood volume in the brain tissues are not the significant factors responsible for the elevation of cisternal cerebrospinal fluid pressure and increase in brain bulk observed when distilled water is administered.

**Cerebrospinal Fluid Protein Content.** Increase in brain bulk and pressure may also be produced by an increase in volume of cerebrospinal fluid, particularly if it is in communication with, or indeed identical with, the extracellular fluid of the brain.²⁻¹² It was reasoned that an increase in volume of cerebrospinal fluid, if on the basis of dilution with water, might be reflected in a change of the existing protein content of the fluid. As a consequence of these considerations, the cisternal protein levels⁹ were determined in two series of animals, to one of which distilled water was given.

It was found that among the 10 control animals the protein values of cisternal cerebrospinal fluid averaged $55.3 ± 23.9$ mg. per cent, whereas among the 8 animals to which water was administered the values had a mean of $17.2 ± 4.5$ mg. per cent. The probability figure of this difference being chance is <.01. This is a helpful clue that the volume of cerebrospinal fluid may have increased and hence contributed to the raised cerebrospinal fluid pressure and apparent increase in brain bulk. Further support for such an increase in volume of cerebrospinal fluid is derived from subsequent measurements of the total volume of the cerebrospinal fluid by drainage techniques which document a significant increase in volume of cerebrospinal fluid per unit body weight when water is administered.

**Water and Electrolyte Content.** The observations of Alexander and Looney¹ are particularly interesting. Measuring the differential water content of gray and white matter in 22 autopsied brains, these workers reported their lowest value in the white matter of a so-called “edematous” brain, and their highest percentage of water in the moderately atrophic brain. They found no correlation between water content and histologic criteria of edema or atrophy, nor was there any correlation between water content and specific weight of the brain.

Pilcher,¹³,¹⁴ in studying the effects of injury upon dog brains, measured the water content of gray and white matter by the dessication method. He considered any change in average findings as great as 1 per cent of fluid content beyond the probable limits of error of the method. White et al.²² considered such methods insufficiently sensitive, but the results of Eichelberger and associates³⁻⁴ and Windle et al.²₃ were considered evidence in favor of proceeding with such measurements.

Experiments were designed to measure the water and electrolyte content of cat brain tissue under the conditions heretofore described.

Upon completion of experimental observations, samples of cisternal cerebrospinal fluid and arterial blood were drawn and the calvarium was quickly removed; the brain stem was severed at the bony tentorium. The brain, removed while the animal was still breathing, was blotted of excess fluid, divided in the midsagittal plane, and stripped of the overlying pia-
arachnoid. Gray matter and white matter were separated by blunt dissection; samples, approximately 1 gm. in weight, of the moist tissue from each were measured for water content by drying to a constant weight (48 to 96 hours) in an oven at 100°C. Equal samples from the opposite moist hemisphere were weighed and homogenized with a detergent, “Sterox S.E.”* and subjected to analysis for sodium and potassium via the Beckman (Model DU) flame spectrophotometer and for chloride via the Beckman (Model B) spectrophotometer. The water content in the brains of the animals in these groups is shown in Table 2.

It was observed that immediately following completion of the water drip there was a significant increase in the water content of the gray matter and a significant decrease in water content of the white matter. If the animals were observed for 60 minutes after cessation of the intravenous drip, there was a significant increase of water content in gray matter alone.

**Antidiuretic Hormone.** The effects of antidiuretic hormone on the water content of the brain in the face of the above described water load were studied under the following experimental conditions:

Two groups of animals (5 in each group) received 1 unit of “pitressin” tannate in oil intramuscularly on the day of the experiment and on each of the 2 immediately preceding days. All animals received distilled water intravenously in the dose and at the rate given in the previously described experiments. One group of animals was sacrificed at the completion of infusion and the other at the completion of a 60-minute postinfusion observation period. The starting pressures in the cisterna magna of the animals to which pitressin tannate had been given were in the same range as the control animal pressures. The pitressin in no way altered the previously described cisternal pressure response when water was administered.

The water content of the gray matter in both sets of pitressin-prepared animals was significantly increased above that in the normal control series, approximating the change seen in the animals which received water without prior preparation with the hormone. There was no significant change in the white matter (Table 3).

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* Monsanto Chemical Company.
TABLE 3

Water content of brain in pitressin-prepared animals

<table>
<thead>
<tr>
<th></th>
<th>No. of Animals</th>
<th>Gray Matter (per cent)</th>
<th>White Matter (per cent)</th>
<th>P—with Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>10</td>
<td>80.80±0.4</td>
<td>71.60±1.4</td>
<td></td>
</tr>
<tr>
<td>I.V. water with</td>
<td>5</td>
<td>80.77±0.4</td>
<td>71.54±0.7</td>
<td>&lt;0.05&gt; .01</td>
</tr>
<tr>
<td>pitressin</td>
<td></td>
<td></td>
<td></td>
<td>&gt; .05</td>
</tr>
<tr>
<td>I.V. water with</td>
<td>5</td>
<td>80.94±0.2</td>
<td>71.81±1.6</td>
<td>&lt; .01</td>
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<tr>
<td>pitressin plus 60</td>
<td></td>
<td></td>
<td></td>
<td>&gt; .05</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

VOLUMETRIC STUDIES

Being able to judge the significance of the water content in the "swollen" brain relative to observed pressure increase required elucidation of the relationship which would exist between mass (volumetric) encroachment on the intracranial space and the cisternal cerebrospinal fluid pressure. Alexander and Looney1 expressed the difference between brain volume and skull capacity in man as a percentage of skull capacity. Edema was considered present if the figure were below 4 per cent and atrophy if above 9 per cent. White et al.21,22 measured the capacity of the cat skull and brain volume and then divided the difference between the two by the skull capacity to obtain a differential index of brain volume. They found that the brain swelling which they produced reduced the cerebrospinal fluid space from 8 to 2 per cent. Pilcher13,14 determined that in dogs a 1 per cent increase in brain weight was the limit beyond which the cerebrospinal fluid pressure would rise.

Taarnhøj,18 using indirect reasoning, calculated that in man an increase of only 1/1000 ml. in cerebrospinal fluid was required to raise the pressure in the fluid from 100 to 200 mm. H₂O. It should be noted, however, that he considered the cerebrospinal fluid system as a rigid, nontamboured chamber.

The following experiments were undertaken: A series of cats was prepared in similar fashion to those to which water was administered. After the calvarium had been uncovered, a 0.5 cm. opening of the skull over the left hemisphere permitted the introduction of a collapsed condom balloon with a capacity approaching 5.0 ml.; the balloon was placed into the extradural space and attached to a needle through which measured amounts of colored fluid could be instilled via a micrometer-manipulated syringe. After fixation of the balloon, a stable pressure record was observed prior to the start of the balloon inflation. (The stable pre-inflation cisternal cerebrospinal fluid pressures averaged 100 mm. H₂O.) The easily distensible balloon was inflated as close as possible to 250 mm. H₂O pressure above the starting pressure. The running pressure was maintained (with some fluctuation attendant upon balloon inflation) at an average of about 350 mm. H₂O. The goal was to maintain this pressure for 30 minutes.

The balloon inflation was designed to produce a pressure that corresponded as closely as possible to the maximum excursions of pressure seen when the animals were given water intravenously, i.e., an absolute increase of 250 mm. H₂O. It was
hoped that by choosing this figure certain comparisons might be made between the animals to which water was administered and those undergoing compression. The 30-minute period of compression was chosen because it corresponded closely to the average time required to administer the distilled water drip in the dose and rates noted.

*Intracranial Volume Determinations.* Sixteen of the initial 29 animals undergoing balloon compression were studied with respect to the relationship of pressure elevation produced by the balloon and volume of the intracranial chamber (supratentorial volume). The volume of this space was determined by enlarging the opening through which the balloon had been inserted, opening the meninges, and with strong suction removing all brain substance back to the incisura of the bony tentorium. The volume of the chamber was measured 3 times with fluid and the average of these measurements was taken.

The mean figure for the intracranial content so determined in 16 animals was $20.2 \pm 2.3$ ml. The total fluid required to fill the balloon and maintain the pressure desired to 30 minutes averaged $2.0 \pm 0.9$ ml. This was 4 to 5 times the volume needed to produce the initial deflection of 250 mm H$_2$O at the start of each study (0.45 ml.). On the basis of the volume of fluid required to produce the initial rise of 250 mm H$_2$O in cisternal fluid pressure, it could be calculated that a 1 per cent increase in the intracranial volume could produce an average rise in cisternal pressure of $1.8$ mm H$_2$O. Conversely, to produce a pressure rise of 100 mm H$_2$O, a 0.9 per cent increase in intracranial volume was required. Such relationships between pressure and volume could be considered to hold true only at the instant of volume change and would have little meaning with respect to maintenance of prolonged compression; it required between 4 and 5 times as much balloon fluid to maintain the same pressure for 30 minutes as was required to produce the initial rise in pressure.

Ten animals on which no pressure measurements were made were anesthetized with intravenous pentobarbital sodium. The top of the calvarium was cut with a small electrically driven dental disc and the brain was removed. The brain was blotted of excess fluid and quickly weighed. It was then immersed in fluid to determine brain volume by measurement of the displaced fluid. The volume of the intracranial space was then measured as outlined in the earlier experiments (Table 4).

<table>
<thead>
<tr>
<th>Volumetric measurements</th>
<th>No. of Animals</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain volume</td>
<td>9</td>
<td>$19.1 \pm 2.0$ ml.</td>
</tr>
<tr>
<td>Brain weight</td>
<td>10</td>
<td>$20.5 \pm 0.9$ gm.</td>
</tr>
<tr>
<td>Intracranial volume</td>
<td>10</td>
<td>$21.0 \pm 1.3$ ml.</td>
</tr>
</tbody>
</table>
In the 9 animals in which brain volume was measured, the difference between this measurement and intracranial volume averaged 2.1 ml. or 10 per cent of the intracranial volume. This percentage is in the same order of magnitude as the observed and calculated increase in volume required to maintain elevation of cerebrospinal fluid pressure by balloon compression for 30 minutes and water administration, respectively (2.0 ± 0.9 ml).

From these observations, it is calculated that during acute brain compression a rise of 100 mm. H$_2$O cisternal cerebrospinal fluid pressure required approximately a 0.9 per cent increase in (or encroachment on) intracranial volume. The average rise in cerebrospinal fluid pressure observed when distilled water was administered was 200 mm. H$_2$O above the pre-injection pressure. Sufficient water to increase the volume 1.8 per cent (0.9 per cent per 100 mm. H$_2$O) would, therefore, be required. Such a percentage would average 0.018×21.0 ml. (average intracranial volume) or 0.38 ml. This amount of water would represent an increase of 1.9 per cent of brain wet weight (20.5 gm.). Since the water content of the brain lies between 71.6 per cent (white matter) and 80.3 per cent (gray matter), the water content would have to rise 2.5 per cent to account for the pressure increases observed. As has been noted previously, no rise of such magnitude was observed in the alterations of water content in these experiments. If the same volume of water were needed to maintain the same pressure for the full 30 minutes, as was produced by the balloon, it would amount to a 10 per cent increase.

In brief, the observed phenomenon of brain swelling attendant upon the administration of distilled water intravenously could not be accounted for satisfactorily by the small increase in the water content of either gray or white matter or both. Such findings are in accord with the views of Alexander and Looney\(^1\) who concluded that cerebral edema* was not so much an absolute increase in water as a shift in its physical-chemical association. Pilcher\(^{13,14}\) also found that the small amount of increased water in the gray matter which he found in dogs with concussion was not proportionate to the increase in cerebrospinal fluid pressure that he observed. Eichelberger and Richter\(^4\) also suggested that the extracellular phase of brain tissue is not a single aqueous phase and that some of the fluid is in the myelin. Fishman\(^6\) considered that the level of cerebrospinal fluid pressure was influenced more by a systemic expansion of the volume of the total body water than by expansion of limited compartments, such as extracellular fluid. From our studies it is suggested that the volume of cerebrospinal fluid may play a more important role in the observed phenomenon than brain water itself.

**MECHANICAL COMPRESSION**

It was noted that among the many groups of animals receiving distilled water intravenously (97 animals) with an attendant rise in cerebrospinal fluid pressure, there was but 1 death under the acute conditions of our ex-

* Italics are ours.
experiments. Conversely, the production of similar pressure rises by the balloon method was attended by numerous deaths (19 out of 67). We therefore extended our observations on the compressed animals as follows:

Water Content. Eleven cats were prepared for balloon compression studies as outlined above. At the completion of 30 minutes of compression, the fluid was released from the balloon and intravenous distilled water was administered in the same dose and at the same rate as in the preceding experiments. No significant changes in the water content of gray or white matter of the brain were observed in animals undergoing balloon compression for 30 minutes with immediate sacrifice. There was a significant decrease in water content of both gray and white matter of animals in which brains were compressed, released from compression, and analyzed 60 minutes later (Table 5).

Although there was less water in the brain, the pressure observed in the great cistern after deflation of the balloon ranged from 50 mm. H$_2$O to 250 mm. H$_2$O, as compared with the range of 50 mm. H$_2$O to 162 mm. H$_2$O pre-inflation, bearing, therefore, no apparent relationship to water content.

In spite of the high cerebrospinal fluid pressures generated under such circumstances (Table 7), water changes were noted only in the gray matter of animals sacrificed immediately after conclusion of the water drip. At this time, the water content of the gray matter rose in the experimental animals as compared with the control animals ($P < .05$).

Chemical Studies. The significant alterations in the chemical analyses of the experimental animals are presented in Table 6. The most significant finding was in the alteration observed in the sodium and potassium content of the brain.

The potassium content in the gray and white matter of the brain was raised significantly above that of the control animals: 1) when distilled water was administered; 2) when the brain was compressed and a delay followed before sampling; and 3) when distilled water was given to pitressin-prepared animals with a 60-minute delay before sampling.

The sodium content of the gray matter fell in groups 1 and 2, and the sodium content of the gray and white matter fell in animals treated with pitressin (group 3).

The potassium content rose significantly in the white matter alone: 1) when the brain was compressed (without delay before sampling); 2) when

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Water content of brain in animals treated with compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Animals</td>
<td>Gray Matter (per cent)</td>
</tr>
<tr>
<td>Controls Compression—observed for 60 min.</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 6

**Chemical analysis of brain significant alterations**

<table>
<thead>
<tr>
<th></th>
<th>Gray Matter</th>
<th>White Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Mean</td>
<td>61.8</td>
<td>75.5</td>
</tr>
<tr>
<td>σ</td>
<td>9.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Distilled water (no wait)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mean</td>
<td>47.6</td>
<td>82.0</td>
</tr>
<tr>
<td>σ</td>
<td>8.0</td>
<td>4.0</td>
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<tr>
<td>“t” test with control series</td>
<td>3.74</td>
<td>2.27</td>
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<tr>
<td>Distilled water (wait)</td>
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<td></td>
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<tr>
<td>No.</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>50.7</td>
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<tr>
<td>σ</td>
<td>2.6</td>
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<tr>
<td>“t” test with control series</td>
<td>3.79</td>
<td></td>
</tr>
<tr>
<td>Physiological salt solution (no wait)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>53.0</td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td>Water and pitressin (no wait)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.5</td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>2.39</td>
<td></td>
</tr>
<tr>
<td>“t” test with control series</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water and pitressin (wait)</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.1</td>
<td>94.3</td>
</tr>
<tr>
<td>σ</td>
<td>4.9</td>
<td>7.6</td>
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<tr>
<td>“t” test with control series</td>
<td>3.94</td>
<td>3.85</td>
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<td>Compression (no wait)</td>
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<td>No.</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>47.5</td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>“t” test with control series</td>
<td>2.75</td>
<td></td>
</tr>
<tr>
<td>Compression (wait)</td>
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<td></td>
</tr>
<tr>
<td>No.</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49.1</td>
<td>97.0</td>
</tr>
<tr>
<td>σ</td>
<td>5.0</td>
<td>8.9</td>
</tr>
<tr>
<td>“t” test with control series</td>
<td>2.81</td>
<td>3.36</td>
</tr>
<tr>
<td>Compression and water (no wait)</td>
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<td></td>
</tr>
<tr>
<td>No.</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49.8</td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>“t” test with control series</td>
<td>2.79</td>
<td></td>
</tr>
</tbody>
</table>

All results in milliequivalents.

“t” = 2-sided test for t at 5% level of significance.

distilled water was administered, followed by a delay before sampling; and 3) when the brain was compressed and distilled water was administered without delay before sampling.

Once, again, a lowered sodium content in the gray matter was observed.
in every instance (1, 2, and 3). (Lowered sodium content in the gray matter was observed in other circumstances without significant changes in potassium content, i.e. with the administration of physiological salt solution, with and without a delay before sampling.)

**Electrolyte—Water Comparison.** These data were studied for an expression of any relationship that might be found between the induced rises of cerebrospinal fluid pressure, the chemical analysis of the brain, and the water content of the brain. It would appear that when the water content of the gray matter increases there is a fall of sodium content in these animals. No other consistent relationships were found.

**BRAIN COMPRESSION DYNAMICS**

The first group of 29 animals underwent brain compression by balloon to a maximum of 30 minutes. A representative tracing of surviving animals is shown in Fig. 3. Five of the 29 animals died as a result of the compression in less than 30 minutes after the balloon was inflated and they died with final cisternal pressures averaging 330 mm. H$_2$O. The pattern of the tracing before death was similar in each case. After a small balloon increment had raised the pressure to the desired level (250 mm. H$_2$O above the starting pre-inflation pressure), the cerebrospinal fluid pressure, instead of stabilizing, continued to rise and within seconds, or perhaps simultaneously, was accompanied by slower, deeper respiration, heightened pulse pressures, raised blood pressure, and short periods of apnea; this was soon followed by collapse of all pressures and death. Some of these changes are illustrated in Fig. 4. The volume of the final triggering increment of fluid introduced into the balloon was always small, and the sequence of events leading to collapse lasted,

![Fig. 3. Split tracing of cerebrospinal fluid pressure (top line) and arterial pressure (bottom line) at start and completion of 30-minute period of balloon compression. Note stable arterial record.](image-url)
on the average, less than 2 minutes. Alterations in vital signs presaging the collapse were not anticipated by abnormalities of the preceding record and were in contrast to the stable picture observed at the onset of each study when the balloon was initially inflated to produce the desired elevation and at which time no animal died. The acuteness and the duration of compression would, therefore, seem to be factors, and in these 5 animals the compression lasted 8, 12, 20, 23 and 25 minutes before death occurred.

Another 5 animals from the group of 29 demonstrated signs of dissolution coincident with the end of the 30-minute compression period. In 3 of these animals, delayed “triggering” was noted during the compression; i.e. the cerebrospinal fluid pressure, having been maintained at the desired height and, without any new increment of fluid immediately preceding, rose no more than 25 mm. H₂O before the blood pressure changes described above took place (Fig. 5). In these 3 animals the balloon was deflated after onset of alterations in vital signs, but the animals died.

Seven animals survived and tolerated the 30-minute compression period, after which time the brains were removed for analysis.

The final 12 of the 29 animals survived the 30 minutes of compression and were observed for varying periods of time after release of the balloon. Six of these were followed for a period of 60 minutes without adverse effect (Fig. 6). Four additional animals completed observation periods of 15 to 30 minutes without adverse effect, at which time the experiments were terminated. Two animals died 14 minutes and 35 minutes after release of the balloon. In each of these animals, there had been alterations in vital signs dur-
Fig. 5. Tracings of cerebrospinal fluid pressure (top line) and arterial pressure (bottom line) during 30 minutes of balloon compression. (A) Onset with stable record. (B) Spontaneous rise after 23 minutes of compression. (C) Completion of compression. Note rise in cerebrospinal fluid pressure prior to deflation, with death after 3 minutes.

The alterations in blood pressure, pulse and respiratory rate, volume and regularity were not observed (in the face of stable anesthesia) with the rises in cisternal pressure attendant upon inflation of the balloon until a fairly sharp end point was reached, punctuated by the train of events described and illustrated above. In several of the animals
doomed to die from the effects of the pressure, continued rises of cisternal fluid were noted following cessation of filling the balloon. This continued rise in cerebrospinal fluid pressure after distention of the balloon ceased often was a premonitory sign of the onset of the fatal triggering during the succeeding few increments.

**Postcompression Observations.** The records of the 12 animals that underwent 30 minutes of brain compression and were observed for periods up to 60 minutes after the balloon was released were studied for evidence of “secondary” rises in cerebrospinal fluid pressure after release of the balloon which might be indicative of postcompression swelling. Four of the 12 animals demonstrated postdeflation pressure elevations: In 1 animal the rise was caused by lightening of the level of anesthesia; 1 animal demonstrated signs of impending collapse from a pressure of 500 mm. H$_2$O, at which time the balloon was deflated; the other 2 animals demonstrated an initial fall to pre-inflation pressure upon release of the balloon, but this was followed by a slow pressure rise to about 150 mm. H$_2$O above the pre-inflation “normal” pressure. These elevated pressures were sustained throughout the 60-minute observation period (Fig. 7). There were no clear explanations forthcoming for these rises.

**Brain Compression Plus Intravenous Administration of Distilled Water.** The combination of brain compression and intravenous administration of distilled water produced the maximum pressure elevations observed in any of the various series and was certainly the most lethal process.* It proved

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* Such elevations did not occur if physiologic salt solution were substituted for distilled water (Fig. 8).
more lethal than compression alone, and the frequency of deaths was in striking contrast to that obtained when animals received water alone (Fig. 9). The maximum pressures generated with the administration of water were observed near the conclusion of the drip and the mean pressure for 11 animals at that time was 479 mm. H₂O. Of those animals that survived sufficiently to be observed after the completion of the intravenous drip (5 ani-

Fig. 7. Split tracing of cerebrospinal fluid pressure (top line) and arterial pressure (bottom line) demonstrating rise in cerebrospinal fluid pressure after balloon compression: survival.

Fig. 8. Split tracing of cerebrospinal fluid pressure (top line) and arterial pressure (bottom line) demonstrating effect of I.V. physiologic salt solution on cerebrospinal fluid after 30 minutes of balloon compression.
mals), it was noted that in 4 the pressures continued to mount and reached the maximum levels seen in any animal, often exceeding the graph paper limit of 650 mm. H$_2$O.

In the first 6 of the animals that underwent brain compression followed by instillation of water, administration of the latter coincided with a gradual rise in cerebrospinal fluid pressure to a level varying from 300 mm. H$_2$O to 500 mm. H$_2$O above the pressure immediately after the balloon was deflated. Two animals decompensated and died at the completion of the intravenous drip; the cerebrospinal fluid pressure in each registered 650 mm. H$_2$O. Spontaneous drops in cerebrospinal fluid pressure of over 300 mm. H$_2$O occurred on several occasions in 1 of these animals (Fig. 10). Such variations suggested intracranial adjustment, shift, or other compensatory mechanisms.

The surviving 5 animals were observed to a maximum of 60 minutes after the intravenous water had ceased. In each, the excessively high pressure observed at the completion of water drip was maintained and often exceeded, reaching levels of 625 mm. H$_2$O in the final minutes before other alterations in vital signs and decompensation occurred. Only 2 of this group of 5 animals survived the full 60 minutes of postwater observation. In 1 animal interesting fluctuations of cerebrospinal fluid pressure, suggestive of an intracranial shift and mechanical adjustment, may have saved the animal’s life (Fig. 11).

A summary of the comparative pressure data of the various groups of animals studied is presented in Table 7.

Discussion of Compression Dynamics. 1. The balloon-compression method of raising the intracranial pressure (cisternal pressure) was more lethal and
less well tolerated by the animals than was the distilled-water method. Each produced comparable rises in pressure. It is probable that at least one explanation for this observation is the adverse effect of acute local compression of the brain with its attendant shifts of the brain substance and disproportionate suffering of vital brain centers (Fig. 13) and vascular elements.\textsuperscript{11} On the other hand, the intravenous administration of water may produce its effect uniformly without such shifts and thereby utilize the intracranial space more efficiently without compromising cerebral function. The "triggering" effects of balloon inflation and the continued rises of cerebrospinal fluid pressure following small balloon increments observed frequently in the
compression series suggested "impaction" or incarceration and herniation of tissue, perhaps temporary at the onset but becoming permanent with further rises in cerebrospinal fluid pressure (Figs. 12 and 13).

2. Brain compression followed by the intravenous administration of distilled water was the most lethal combination in the series. It was in the group of animals so treated that the highest cisternal pressures were ob-

**TABLE 7**

*Pressure relationships*

<table>
<thead>
<tr>
<th>No. of Animals</th>
<th>Cisternal Base Pressure (mm. H₂O)</th>
<th>Maximum Pressure Observed (mm. H₂O)</th>
<th>Pressure at End of Drip (mm. H₂O)</th>
<th>Final Pressure (mm. H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control animals</td>
<td>10</td>
<td>106 ± 39</td>
<td>133 ± 65</td>
<td>116 ± 72</td>
</tr>
<tr>
<td>I.V. physiologic salt solution</td>
<td>10</td>
<td>68 ± 39</td>
<td>134 ± 43</td>
<td>123 ± 42</td>
</tr>
<tr>
<td>I.V. distilled water @ 40 ml./kg.</td>
<td>10</td>
<td>68 ± 23</td>
<td>248 ± 85</td>
<td>248 ± 85</td>
</tr>
<tr>
<td>I.V. distilled water—60-min. observation</td>
<td>10</td>
<td>99 ± 52</td>
<td>338 ± 114</td>
<td>318 ± 85</td>
</tr>
</tbody>
</table>

Compression with balloon 250 mm. H₂O above baseline

<table>
<thead>
<tr>
<th>No. of Animals</th>
<th>Cisternal Base Pressure (mm. H₂O)</th>
<th>Maximum Pressure Observed (mm. H₂O)</th>
<th>Pressure at End of Drip (mm. H₂O)</th>
<th>Final Pressure (mm. H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression—I.V. water 60-min. observation</td>
<td>6</td>
<td>127 ± 96</td>
<td>546 ± 27</td>
<td>546 ± 27</td>
</tr>
<tr>
<td>Compression—I.V. water—60-min. observation</td>
<td>5</td>
<td>62 ± 38</td>
<td>537 ± 193*</td>
<td>415 ± 144</td>
</tr>
</tbody>
</table>

* One animal = 188, other 4 = 625.
† One animal = 0, other 4 = 625 (?needle block).
These pressures were consistently higher than those found in animals to which water had been administered without compression. It was only in the former group that "spontaneous" drops in high cisternal pressure were seen. Such drops, of perhaps 200 mm. H$_2$O, occurred abruptly, lasted for a minute or so, and were followed by restitution of high pressure (Figs. 10 and 11). It may be surmised that the prior compression had dislodged and possibly impacted portions of brain substance which, when subjected to the mechanism of pressure rise with administration of water, could not adjust readily and hence produced lethal effects on vital areas. If shifts of substance

Fig. 12. Tracing of cerebrospinal fluid pressure (top line) and arterial pressure (bottom line) demonstrating triggering effect of small balloon increment during balloon compression.

Fig. 13. Photograph of cat brain fixed in situ after 30 minutes of balloon compression (balloon still inflated at time of fixation) as utilized in this study. (A) Superior view. (B) Coronal section across center of compression. Note distortion of midline structures and absence of contusion.
or “disimpaction” occurred, therein might lie the explanation for the spontaneous drops of pressure.

3. The high pressures associated with brain compression plus administration of water could not be explained on the basis of a summation of postcompression swelling plus water, for few examples of secondary rises in pressure after deflation of the balloon were observed in the compression series alone.

4. Alterations in vital signs, when they occurred with these methods of producing rises in cerebrospinal fluid pressure, signified impending collapse, were not observed until decompensation was imminent, were rarely reversible, and led to death within a few minutes. There was no indication of a sensitive relationship between cerebrospinal fluid pressure *per se* and pulse, respirations, and blood pressure. Time (the duration of the pressure-raising mechanisms) was an important element.

5. The heightened pressures observed after brain compression plus water were maintained after the water drip ceased, in contrast to the pressures observed over similar periods in animals to which only water was given. The former pressures were seen to rise above the maximum pressure noted during the water drip. The pressures obtained in association with the water exceeded the pressures caused by inflation of the balloon alone in 10 of 11 animals. The average excess rise above the balloon pressure for the 11 animals was 190 mm H$_2$O. On the basis of the measurements previously noted above, such an added rise might be accounted for on the basis of encroachment upon the intracranial volume of roughly 1.5 per cent, which in the average cat would require in volume about 0.3 ml. It is readily appreciated, however, that such an increase in volume would not sustain this rise, and that the mass (of fluid) responsible would have to be considerably more than 0.3 ml. Perhaps, for a 30-minute sustained rise, about 1.2 ml. (4×the initial amount) might be needed.

It was found that whereas techniques of brain compression were often lethal, especially when water was administered to the animals, the addition of artificial respiration to the technique seemed to protect the animals from dying. This salutary effect of artificial respiration is not fully understood. It is possible, however, that it adds a more efficient pulsatile quality to the intracranial fluids such that the animals may adjust more readily and utilize more completely the intracranial space before irreversible impaction occurs (Fig. 1).

**SUMMARY AND CONCLUSIONS**

The phenomenon of brain swelling as induced by intravenously administered distilled water has been studied experimentally.

In the cat, distilled water given intravenously produces a consistent elevation in cerebrospinal fluid pressure, but only an apparent increase in brain volume. Such an increase in pressure and brain bulk is not accounted for by an increase in blood content of the brain, nor is it prevented by the utilization of artificial respiratory techniques in the experimental protocol. Such
techniques do, however, decrease venous pressure and enhance the pulsatile quality of the cerebrospinal fluid dynamics.

The water content of the brain increases in small but significant amounts when water is given, but the increase is insufficient, volumetrically, to explain the rises in cerebrospinal fluid pressure observed.

A significant fall of cerebrospinal fluid protein and an increase in volume of cerebrospinal fluid as measured by drainage techniques are produced by the administration of distilled water suggesting that part, at least, of the mechanism of "brain swelling" associated with water may be on the basis of an increase in volume of cerebrospinal fluid.

The increase in volume in the intracranial space to produce a given rise in cerebrospinal fluid pressure has been measured and expressed quantitatively by the utilization of a balloon to cause compression of the brain. This technique of brain compression permitted a comparison to be made between the effect of rises in cerebrospinal fluid pressure produced by distilled water and the effects of equal rises in pressure produced by acute compression by an extradural mass. Such effects are observed on brain water content, electrolyte content, animal survival, and vital signs.

The combination of compression of the brain and administration of water to produce rises in cerebrospinal fluid pressure in excess of those produced by either one alone reveals alterations in intracranial dynamics which suggest that the phenomenon of diffuse swelling occurring with water utilizes the available intracranial space to maximal efficiency, whereas compression by mass does not. The release or removal of a compressive mass is in itself often ineffective in reversing a lethal train of events resulting in collapse of vital centers, and this is especially true if the brain is swollen into its dislocated state by the water technique. The enhanced pulsatile quality imparted to the cerebrospinal fluid by artificial respiratory techniques may provide a protective mechanism to the animal whereby all parts of the intracranial spaces may be utilized for expansion of the swollen brain.

The author wishes to acknowledge with appreciation the consultative advice of Professor Ralph McKee of the Department of Physiological Chemistry, University of California Medical Center, and the technical assistance of Mrs. Genevieve Armstrong, Mr. William Brathwaite, and Mr. Robert G. Good of the Department of Surgery.

REFERENCES
DISCUSSION*

Dr. Joseph P. Evans: The Program Committee is to be congratulated on the inclusion of these four papers as a unit. I have had the privilege of reading the first three in full and have heard the fourth with great interest.

Reform in our thinking about increased intracranial pressure and its supposed deleterious effects upon the central nervous system is long overdue. "Reform" is a much abused word and usually has a malodorous connotation.

I am sure that Dr. Cushing would have agreed that reforming one's ideas in the light of newer knowledge is one of the essentials of adequate scientific thinking. Reform in the area under discussion this morning really began, as Dr. Thompson pointed out in his paper, with a highly critical and perceptive article by Jefferson Browder and Russell Meyers in which they pointed out that there was a lack of correlation between medical signs and symptoms and the degree of intracranial pressure.

Since then, evidence has continued to accumulate that although increased intracranial pressure...
pressure may accompany deleterious pathological states, it need not be present for clinical effects to be observed, and furthermore, the brain will tolerate very high intracranial pressures, even when rapidly produced, provided that the pressure effects are distributed evenly, as pointed out by Ryder in 1953.

The Ryder studies did not, however, include many observations on effects of increased pressure measured in terms of days or weeks, a body of information which is still, so far as I know, wanting. This is a gap in our knowledge which I hope we may be able to fill in before very long.

The paper of Dr. Stern shows a highly commendable projection of a research plan. Since I had not known exactly what phases of the total paper he would emphasize today, it has been difficult to determine just where to direct my remarks.

I do find myself concerned over his criteria of brain swelling. First, increase in brain bulk, which is certainly a valid approach, although measurement of brain bulk is exceedingly difficult, but second, his statement: "a corresponding rise in cerebrospinal fluid pressure."

Just a decade ago, working with Frank Espey in John Fulton's laboratory, we undertook to produce cerebral swelling in monkeys, laboring under the illusion that continuous recording of intracranial pressure would serve as an index of the degree of brain swelling. Our efforts were abortive, but from the work followed the studies in which Henry Ryder showed that there is no direct correlation between swelling and pressure, so flexible is the relationship between lesion—as for example the balloon that Dr. Stern uses—cerebral tissue, cerebral blood volume and cerebrospinal fluid volume.

Further it was concluded that: "When symptoms or signs of cerebral dysfunction are associated with a change in cerebrospinal fluid pressure or an abnormal fluid pressure, the association results from the effect of the factor or factors common to both the pressure or the dysfunction and not from a causative relation between pressure and dysfunction."

In the light of Dr. Thompson's work, it was somewhat prophetic that the further statement was made: "Certain factors which modify the cerebrospinal fluid pressure may also modify cerebral function by stretching or displacing cerebral tissue." At the time this statement was made we were thinking more of supratentorial displacement of midline structures across the midline, though transtentorial herniation was also evidently in mind.

Dr. Thompson's concept of acute axial displacement is, I am confident, a valid conception as the explanation of cardiorespiratory changes, as he has demonstrated so ingeniously. I should like, however, to record an instance of the deleterious effects of slow displacement to supplement these observations.

I won't go into detail on this, but in the case of a child in whom we performed a hemispherectomy we left the choroid plexus in place, thinking that the cerebral fluid would communicate with the ventricular spaces; however, the foramen of Monro became occluded and gradually, over a period of 6 weeks, this boy's condition deteriorated.

We were slow in recognizing what was going on but at the end of 6 weeks, when we performed a choroid plexectomy on this side, the total picture reversed. I think there is no question of what was happening—the fluid in the right hemicalvarium was acting as a space-consuming lesion and was displacing the brain stem downward through the incisural notch.

The well-documented observations of Dr. Javid on the remarkable effectiveness of urea are certainly very encouraging. That his method will obviate the occasional necessity of applying tentorial section remains to be determined.

DR. WILLIAM B. SCOVILLE: I am happy to be given the privilege of discussing the provocative work of my good friends, Drs. Nulsen and Malina and their co-workers. For some years past I have done a unilateral, inferior, horizontal, temporal lobectomy through a subtemporal decompression extended posteriorly to overlie the petrous ridge, permitting resection of the inferior one-half of the temporal lobe below the level of the temporal horn and extending medially so as to remove by subpial suction the herniated hippocampal gyrus and uncus. Semantically speaking I feel we should label this an incisural herniation of the hippocampal gyrus rather than of the uncus which is the offending member causing compression against
the peduncle. This operation so far has been done on critically ill or moribund patients showing decerebrate rigidity; unilateral dilated fixed pupil spreading bilaterally; failing vital signs with Cheyne Stokes breathing and rising blood pressure; and a contralateral spastic hemiparesis. In 1 case, there was generalized anasarca and renal shutdown and in 2 cases actual respiratory arrest. I presented 4 and 7 cases respectively at the Latin American Congress in 1955 and at the Scandinavian Congress in 1956, and an exhibit at former meetings of the Harvey Cushing Society. These were cases of cerebral trauma, postoperative edema from meningoia, and cerebral hemorrhage. The results have been dramatic with an immediate improvement in the vital signs and over-all condition in those cases in which incisural herniation was found and in those cases in which there was no continuing space-filling lesion, such as hematoma or tumor. Failures have occurred in those cases in which a blood clot and in 1 case a tumor were not located. In such cases, continuing herniation occurred immediately following resection regardless of the amount resected. Four out of 7 patients were restored to a useful existence from a nearly moribund condition.

I am in complete agreement with Nulsen's observations but respectfully wish to differ in technique because of his belief that it is necessary to remove by suction the offending hippocampal gyrus and adjacent inferior temporal lobe to prevent this area from acting as a tamponade, stopping the flow of spinal fluid upwards through the tentorial incisura. In all patients benefited, we have observed a welling up of spinal fluid from beneath the incisura after removing the herniated hippocampus. Tentorial section has been deemed necessary in only half the cases. I am in agreement with Nulsen that it should be done 1 cm. posterior to the petrous ridge in order to prevent damage to the 4th nerve.

In conclusion, I believe that surgical relief of hippocampal incisural herniation in carefully selected cases can result in the same dramatic improvement which is now known to result from tracheotomy under differing criteria.

DR. RUSSELL MEYERS: I join Dr. Evans in expressing appreciation of these provocative papers. However, in regard to the paper delivered by Dr. Collins, I feel impelled to act as devil's advocate in a matter involving logic.

Dr. Collins and his associates section the tentorium cerebelli in a series of cases, the members of which were arbitrarily classified in three groups. In their Group I, 1 patient survived; in Group II, 1; and in Group III, 6. The implication is that the therapeutic variable introduced in this series as contrasted with other more conventional modes of treatment, namely, section of the tentorium and this alone, was responsible for the favorable outcome. (If this is not what the authors meant to imply, it would be hard to comprehend why their paper was offered, since merely to assert, without intention to evaluate for good or ill, that a technical procedure already described and occasionally executed by others had been performed in a new, small series of cases would appear worthy of but trivial notice.) It is just this implication that must engage the student of traumatology. If this implication is to receive inductive logical support, its validity requires starting with some assumption(s) or premise(s).

What would such have to be? Clearly, that without benefit of tentorial section, every patient in the series would have succumbed. But on this point we have no assurance whatever. On the contrary, empirical experience reveals that patients in other clinics who would fit readily into the three categories set up by the authors have on occasion survived without tentorial section. Moreover, the authors employed a number of therapeutic variables other than tentorial section in their cases, for any one of which an equally valid case could be made out, if one chose to do so. This so, it becomes necessary to recognize the implication under examination as a logical non sequitur.

DR. FRANK M. ANDERSON: I have a couple of questions for Dr. Javid. My own experience with urea is very limited, but it is also quite unimpressive, and I wish to ask Dr. Javid two things: One, the time required for the maximum effect and apparently very beneficial effect of this substance. Two, the mode of administration of the drug; that is, does he recommend that it be given by syringe rapidly or by intravenous drip slowly?
Dr. A. Yale Gerol: I don't know if it is because of propinquity to the University of Wisconsin, but we pirated some of the urea away from Dr. Javid. We tried it in most all of our operative intracranial cases and it has been remarkable. One thing I have wondered about is what is happening to the bridging veins on the other side, if the draining veins on my side are so attenuated and stretched.

Dr. John Raff: I'd like to ask Dr. Javid the relative effectiveness of urea given intravenously and orally. Has he carried out any studies to determine loss of electrolytes after administration of urea?

Dr. W. James Gardner: Presumably this shrinkage of the brain that Dr. Javid has reported is caused by the movement of fluid from all the solid tissues into the bloodstream. I would like to ask whether this ever results in any circulatory embarrassment. I would also like to ask whether Dr. Javid has any evidence to indicate that the shrinkage of the tissue is of greater proportion in the brain than in the rest of the body.

Dr. Ernest Sachs, Jr.: This is a question directed to Dr. Stern: In those cases in which there was some triggering mechanism with the small increase in compression, I wonder whether there was microscopic or macroscopic evidence of hemorrhage in the brain stem.

We have had limited use of urea; it has been quite successful and very dramatic. We have had a case of a patient with a recurrent brain tumor done elsewhere and a tight bulging decompression after 0.6 gm. urea/kg. By the time the skin incision was made, the area was entirely sunken! The only thing I am concerned about is some evidence of subdural hematoma when we get inside. I wonder what happens in these enormous subdural spaces, when Dr. Javid closes his wounds.

Dr. William H. Feindel: In order to remove the herniated uncus or hippocampus, one must open the temporal horn of the ventricle and remove a considerable part of the temporal lobe. This in itself gives enough decompressive effect so that the tentorial section may perhaps be unnecessary.

Dr. Arthur Ecker: Dr. Javid, did I see on your first slide that after the beneficial effect of urea the pressure became higher than the original a few hours later; if that is correct, how frequently should urea be given to keep the pressure down?

Dr. Manucher Javid: Perhaps we should have the slide put on again. It went from 525 to 575. I don't consider that rise significant. As a matter of fact, in some patients we have done a pressure measurement for about 3 or 4 hours initially, and you have that much fluctuation in normal patients.

Dr. Arthur Ecker: If we want to keep the pressure low, how frequently do we have to administer urea?

Dr. W. Eugene Stern: Thank you, Dr. Evans, for your comments, and I appreciate your concern about the criteria for brain swelling. We have avoided the term "brain edema" as you see, rather conscientiously, and our criteria for brain swelling are, I am sure, arbitrary.

We have used increase in bulk and increase in cerebrospinal fluid pressure as being the two criteria, with certain provisions, namely that there is no obstructive hydrocephalus, that there is no block to the venous system, that there is no increase in arterial bulk, and that there is no tumefaction. These exclusions would have to be included in the definition.

It is proper to question with what fidelity the tracings which you saw represent in fact what is going on in the intracranial chamber. We have had examples in our animals in which the needle was not recording what was going on. We have had the needle block on occasions in which compression methods were used. In those cases in which the needle did not seem to be sensitive to slight changes in the balloon or other manipulations which we were utilizing, we discarded those animals from any consideration or attempted interpretation.
To Dr. Sachs: We have sectioned and photographed all of the brain stems of these animals. We have not carried out microscopic studies on them. There have been no macroscopic evidences of hemorrhage. We studied the photographs in detail and compared them; we have not been able to demonstrate any structural change macroscopically.

**Question:** Has Dr. Javid any direct observations on the time required for the restoration of brain volume when the urea is given at the operating table?

**Dr. A. Beaumont Johnson:** Three questions directed to Dr. Javid: I was wondering about the limit of administration of urea as a practical therapeutic maneuver, and how long it makes sense to use it.

Second point, certainly hypothermia does affect the decerebrate state. Does urea do the same?

Is there a measurable rebound phenomenon following administration of urea?

**Dr. Manucher Javid:** I wish to thank all the discussants. I shall begin by answering Dr. Anderson's questions which, I believe, were the first. He will recall our correspondence of one year ago. Dr. Anderson had indicated his interest in using urea after the brain is exposed. I pointed out that it would be preferable to give urea prior to opening the dura mater, the reason being my initial experience with the use of urea in surgery, which was always after the brain was bulging. For one thing, we had to wait until reduction took place and, furthermore, the brain shrinkage was not as impressive as subsequent experience showed that it should be. I feel that this is the main reason for Dr. Anderson not obtaining the results experienced by so many neurosurgeons. Another point to re-emphasize: urea should be given as the only solution at the time of surgery. We start urea at the time of skin incision using a large needle, usually a #16, sometimes a #18. The solution should be administered slowly and its rate regulated so that by the time the dura mater is exposed about two-thirds or perhaps three-fourths of the total dose is absorbed. The dose is from 1 gm. to 1½ gm. per kg. body weight. By the time the dura mater is exposed you should have a satisfactory reduction in brain volume. I would let the remaining one-third or one-fourth go in slowly to allow, let us say, exposure and/or clipping of an aneurysm, removal of a pituitary tumor, or part of other tumors, starting "internal decompression," etc. In other words, urea is extremely helpful during the more important part of the operation as far as brain bulk is concerned. Once all of the urea is absorbed, blood, Arfonad or other fluids may follow through the same needle. To date in my experience, this seems to be the best method of administration, especially with "2-inch" craniotomies. But we are still working to determine whether it would be more desirable to start urea when trephinations are inserted before turning the bone flap so that the dura mater is not too slack, thus minimizing epidural bleeding.

Regarding the rate of the injection: I do not like to inject 30 per cent urea rapidly, although rapid injection would also be effective. One does not get the primary rise with urea that one gets with dextrose and sucrose even if it is injected rapidly. If one is using urea in a lower concentration, at about 5 or 10 per cent. then rapid injection would be essential. The rate of administration in pre- and postoperative cases is from 60–100 drops per min.

Dr. Gerol has asked about the bridging veins on the opposite side. When I first used urea I was concerned about these bridging veins. However, experience with craniotomy in 125 patients, under general anesthesia, has persuaded us that this is not a problem with the doses that we have used. This is remarkable especially in procedures that are performed with patients in the sitting position, such as trigeminal rhizotomy (temporal approach) and posterior fossa operations. The only time that we have had opportunity to look at the opposite side of the brain has been in suboccipital craniectomies when both cerebellar hemispheres were exposed, and in bilateral trephinations. To date, we have not seen any subdural hematoma. Furthermore, we have not seen this in any of our patients who came to postmortem examination. I have no doubt that if large doses are used this will occur.

Dr. Raaf's questions (1) relative to effectiveness of urea via stomach tube. Urea is very
effective, but not to the degree achieved by the intravenous route. For obvious reasons, this route should not be used at the time of surgery under general anesthesia, although I am told some neurosurgeons are using it under local. We have used urea frequently pre- and post-operatively by mouth or through a Levin tube. (2) As for electrolyte changes: when urea is used in one or a few doses we have not observed any changes. Outside of our detailed studies with urea nitrogen levels in blood, cerebrospinal fluid and urine, we have not done extensive work with electrolytes, but are planning to do so. In patients who receive urea over a long period of time one would expect changes.

Dr. Gardner's question was with regard to any deleterious effects from dehydration caused by urea. We have not observed any with our method of administration. In 1 patient who, following removal of a recurrent glioblastoma, had been moribund and unresponsive for several weeks, we used a dose of approximately 5 gm. per kg. of body weight. This was in 1500 cc. of 20 per cent solution and was administered in 15 hours. During this period he had an output of 6700 cc. of urine. He was markedly dehydrated. However, in spite of this, with liberal administration of fluid this was corrected and he lived for another 6 weeks. This patient's neurological status was such that even this large amount of urea, which is definitely not a recommended dose, did not change the neurological picture as far as we could determine.

Regarding Dr. Sach's question, personal experience with the use of urea in acute subdural hematomas is limited. I have used it in 3 cases. Urea brought the cerebral edema under control in a fashion to enable us to drain all of the hematoma through two trephines. We always drain our subdural hematomas, so for those who do not put a drain in perhaps urea should not be used. Of course, the use of urea in chronic subdural hematomas is not indicated. Needless to say, urea should not be used in any patient with active intracranial bleeding, since shrinkage of the brain may increase the space into which further bleeding can occur. Years ago, Dr. Browder pointed this out with the use of hypertonic solutions.

At Wisconsin, most of our patients who have increased intracranial pressure have brain tumors. The usefulness of urea during surgery for acute subdural hematoma merits further investigation, especially in hospitals in which a large number of acute head injuries are seen.

Dr. Ecker's question: (1) As far as giving an additional dose of urea when cerebrospinal fluid pressure has returned to original pre-injection level, we have occasionally given another dose of 1 gm. per kg. 12 hours apart. How many times this may be repeated depends on the patient's condition. In the majority of our cases of postoperative cerebral edema 1 or 2 doses have proven sufficient. If we do not see any improvement we do not administer any more urea since it would be pointless to do so. Further experience will determine the best method of repeated administration. (2) As far as concerns hydrocephalus, I must admit that in these hydrocephalics urea was used for measurements (ventricular and lumbar) of cerebrospinal fluid pressure. I am not sure how practical it would be to administer urea in sufficient doses over a long period of time. We have used urea as a temporary measure before proceeding with surgery. For instance, we had an outbreak of measles at one time and we had 3 patients with hydrocephalus who had been exposed. We treated these patients for several days with urea.

With reference to the question as to how soon the brain will be restored to its original volume, this is difficult to evaluate in intracranial surgery in man because after the brain is exposed something is done to it. For instance, a portion of it is removed, some cisternal fluid has escaped, etc., so that any observation would be invalid. I would say that during the average intracranial operation, which lasts from 2-4 hours, the effect of shrinkage is noticeable. Of course, our studies of cerebrospinal fluid pressure show that reduction may last from 3-10 hours with the doses that we have employed.

Dr. Johnson asked (1) how long urea can be used. Half of our patients have received only 1 dose, pre- or postoperatively. One patient has been receiving urea by mouth for the last year in small doses. She has migraine headache. At first she received it in powder form, dissolved in unsweetened grapefruit juice, but because of its disagreeable taste she preferred to receive it in tablet form even though this meant taking large numbers of them. In circumstances in which daily administration of 1 gm. per kg. body weight is desirable, such as in
patients with pseudotumor cerebri, or patients with head injury who have marked cerebral edema, it would be important to keep an accurate record of intake, output, daily blood urea nitrogen levels, etc. One has to treat each case individually.

(2) As to whether urea works the same way as hypothermia, I do not know. My experience with hypothermia is limited. In a few cases in which urea was used with patients under hypothermia, I have a distinct impression that brain reduction was more marked.

(3) With regard to the question whether there is any rebound phenomenon with urea, we have not observed this. We have compared urea with many hypertonic solutions in monkeys. Sodium chloride is the one notorious for this rebound effect and, as you well know, it is discarded.