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The Influence of Urea and Mannitol on Increased Intraventricular Pressure in Cold-Induced Cerebral Oedema

By

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With 5 Figures

Freemont-Smith and *Forbes* (1927) were the first to observe that administration of a hypertonic urea solution reduces the cerebrospinal fluid (CSF) pressure. They found that the CSF pressure in cats diminished considerably after an intraperitoneal injection of a hypertonic urea solution. In 1950, *Smythe* et al. described a urea solution as preferable to glucose in reducing CSF pressure during operations.

Javid and *Settlage* (1956) later introduced the clinical use of hypertonic urea solutions, which has since become widely accepted.

Gradually, however, there were an increasing number of reports on untoward side effects following the administration of hypertonic urea solutions in order to reduce the CSF pressure. These toxic side effects were believed to occur chiefly when the urea was administered in large doses. The side effects described included nausea, vomiting, diarrhoea and disturbances in the electrocorticogram (*Stevenson, Jacobs, Ross, Collins,* and *Randt* 1959), ECG changes (*Bering* and *Avman* 1960), haemoglobinuria (*Javid* and *Settlage* 1956; *Langfitt* 1961) and thrombosis of the vessel through which the urea solution was administered as well as disturbances in the mechanism of coagulation (*Mason* and *Raaf* 1961). Moreover, urea administration was believed to be followed by a rebound effect which increased the CSF pressure to a level above the initial value (*Bering* and *Avman* 1960; *Langfitt* 1961; *Fisher* 1962; *Stubbs* and *Pennybacker* 1960). *Shenkin* et al. (1962) and *Wise* and *Chater* (1962) reported that a mannitol solution was at least as effective as hypertonic urea in reducing CSF pressure, and acted longer. Mannitol was described as having other advantages over urea also. It was described as remaining confined to the extracellular space, rapidly excreted, readily prepared, causing no rebound effect and not contraindicated by existing renal abnormalities.

Buckell (1964) maintained, however, that the actions of urea and mannitol are not strictly comparable. Observations showed that the

administration of 100 g (= 555 m osm) mannitol caused a greater increase in plasma volume than 50 g (= 666 m osm) urea. Mannitol caused a greater and more protracted diminution of plasma sodium and plasma protein concentrations, haemoglobin concentration and haematocrit value. Intravascular haemolysis, albeit slight, was more frequently seen following administration of urea. Moreover, some 40% of the urea is absorbed, whereas mannitol is fully filtered and not absorbed, so that it disappears from the circulation more quickly and consequently has a more intensive diuretic effect. However, its effect on the white matter is less specific than that of urea.

The object of our experiments was to study the influence of urea and mannitol, respectively, on the increased intraventricular pressure resulting from experimentally induced cerebral oedema.

Material and Method

For these experiments we used 22 adult cats anaesthetized by the intramuscular injection of 50 mg phenobarbital per kg body weight. One hour later, the cats received 20 mg pentothal per kg body weight intraperitoneally. Once induced, the anaesthesia was maintained with a nitrous oxide-oxygen mixture; the animals had been intubated and were breathing spontaneously.

A needle was inserted stereotactically into the cella media of the right lateral ventricle, and connected to a Statham physiological pressure transducer P 23 AA. The intraventricular pressure thus measured was recorded on a type-R Offner Beckman dynograph.

During the experiments, arterial and venous blood pressures were recorded via cannulae in the femoral artery and femoral vein. The ECG and respiration were likewise recorded. An opening with a diameter of 13 mm was trephined in the left frontal region; the trephine centre was located 10 mm behind the coronal suture and 15 mm from the midline. The dura mater was left intact. A cooling thermode was inserted into the trephine opening in such a manner that its base was in contact with the dura.

After recording the pressure in the ventricular system for one hour, we pumped methanol chilled to a temperature of — 30° C through the thermode for 10 minutes. The thermode was left in situ throughout the experiment lest the intracranial pressure be disturbed.

The cooling produced a cortical lesion which was sharply defined, slightly swollen and of darker colour than the adjacent area. The histological features of the cortical lesion resembled those of a recent infarct. Particularly in the cerebral cortex, and to a lesser degree in the white matter, the chilled area contained lesions of the vascular wall through which leakage of fluid occurred. The fluid was PAS-positive and probably moved from the cortex to the white matter (*Beks, Ter Weeme, Ebels, Walter,* and *Wassenaar* 1965).

Occurrence of the cold-induced lesion was followed by oedema, giving rise to an increase in intracranial pressure. The development of the cerebral oedema led to displacement of brain masses and compression of the brain stem. This caused ECG changes and affected respiration and arterial blood pressure. The intraventricular pressure attained its maximum value about 20 minutes after the onset of symptoms indicating compression of the brain stem. At this time the arterial pressure showed a marked increase, and respiratory arrest occurred. Immediately afterwards the intraventricular pressure

decreased, as did the blood pressure, and the animal died unless measures were taken to prevent this.

We studied the influence of an intravenously administered hypertonic urea solution and a mannitol solution, respectively, on the intraventricular

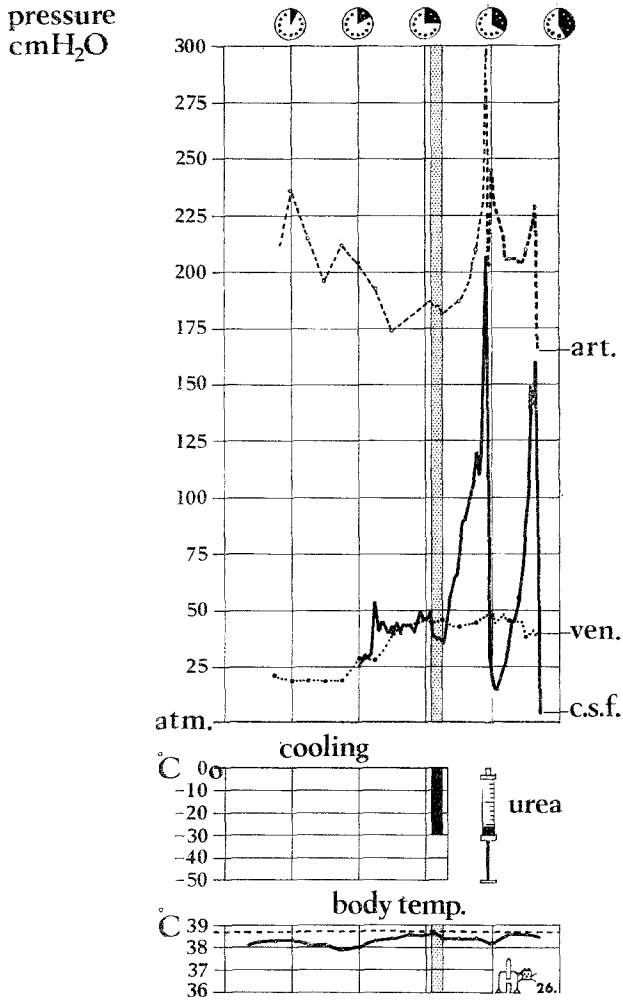

Fig. 1. Course of intraventricular pressure, arterial and venous blood pressure during development of cerebral oedema and after intravenous injection of hypertonic urea solution.

pressure in these test animals (Fig. 1; Fig. 2). The doses administered corresponded with those used clinically, i. e. 3.3 ml urovert (30% urea in 10% invert sugar) per kg body weight, or 8 ml of a 20% mannitol solution per kg body weight. The solutions were injected within 4 minutes, beginning after respiratory arrest had lasted 1 minute (after which the test animal's breathing was artificially controlled).

The test animals were divided into the following groups.

1. Five animals were given hypertonic urea solution intravenously at the above mentioned dosage when intraventricular pressure attained its maxi-

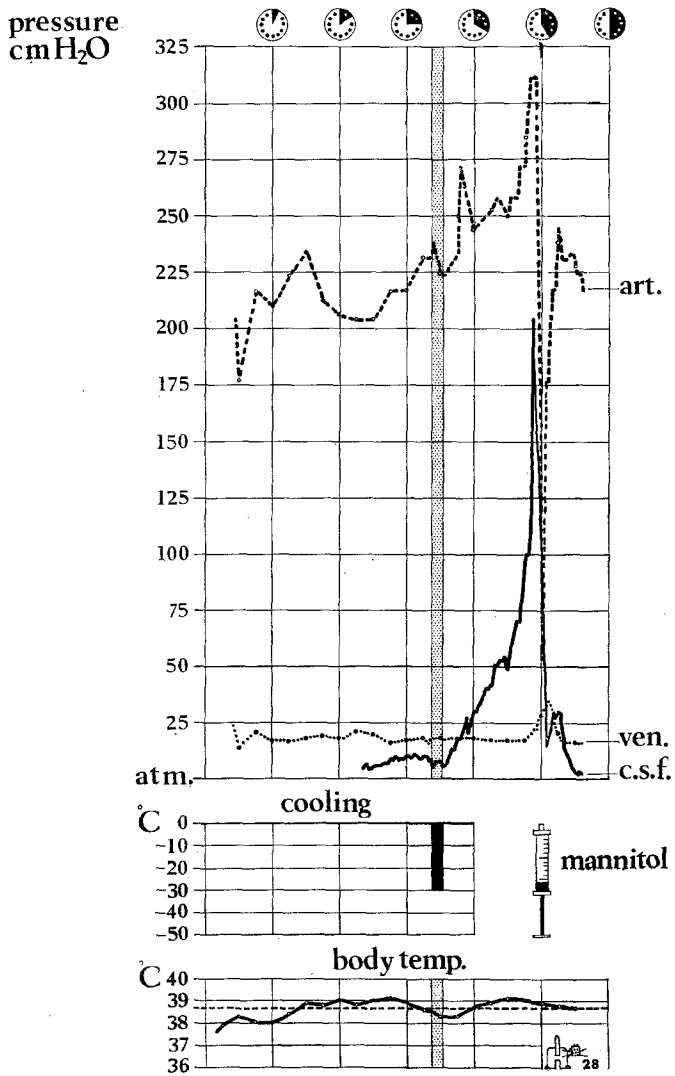

Fig. 2. Course of intraventricular pressure, arterial and venous blood pressure during development of cerebral oedema and after intravenous injection of hypertonic mannitol solution.

mum; they were then sacrificed when the intraventricular pressure started to rise again after having reached its minimum value.

2. Four animals were given hypertonic urea solution intravenously when

the intraventricular pressure attained its maximum, after which a second compression was awaited.

3. Five animals received hypertonic mannitol solution intravenously at the abovementioned dosage when intraventricular pressure attained its

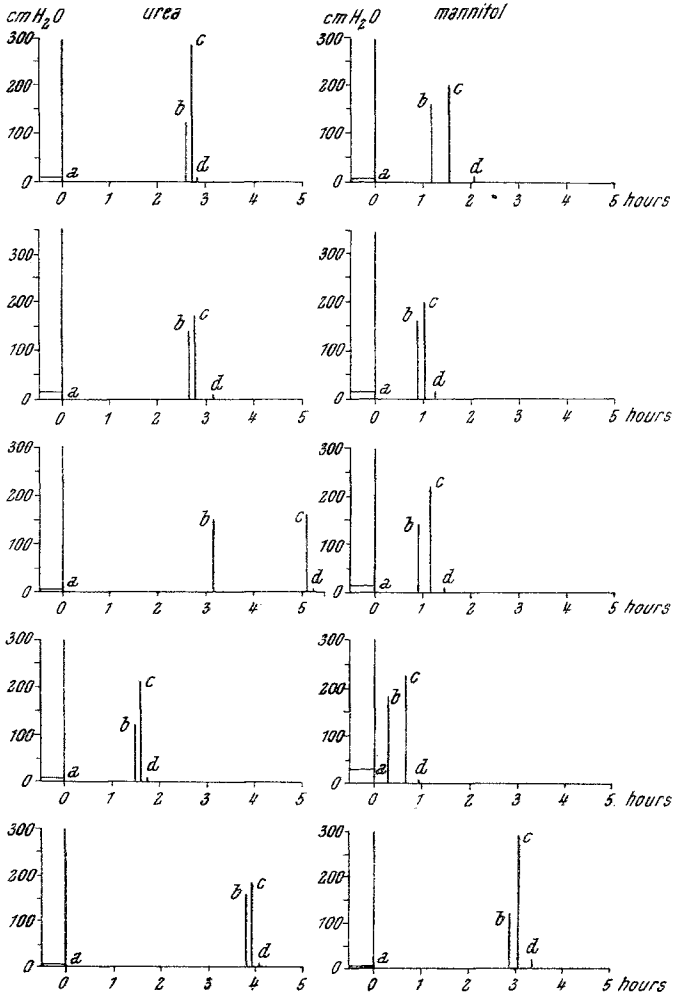

Fig. 3. *a* Initial value of intraventricular pressure, *b* indicates time of onset of respiratory disturbances and the intraventricular pressure recorded at that moment, *c* indicates respiratory failure and the intraventricular pressure at that moment, *d* the lowest intraveutricular pressure recorded following administration of urea or mannitol.

maximum; they were sacrificed when the intraventricular pressure started to rise after having reached its minimum value.

4. Eight animals received hypertonic mannitol solution when the intraventricular pressure attained its maximum value, after which a second compression was awaited.

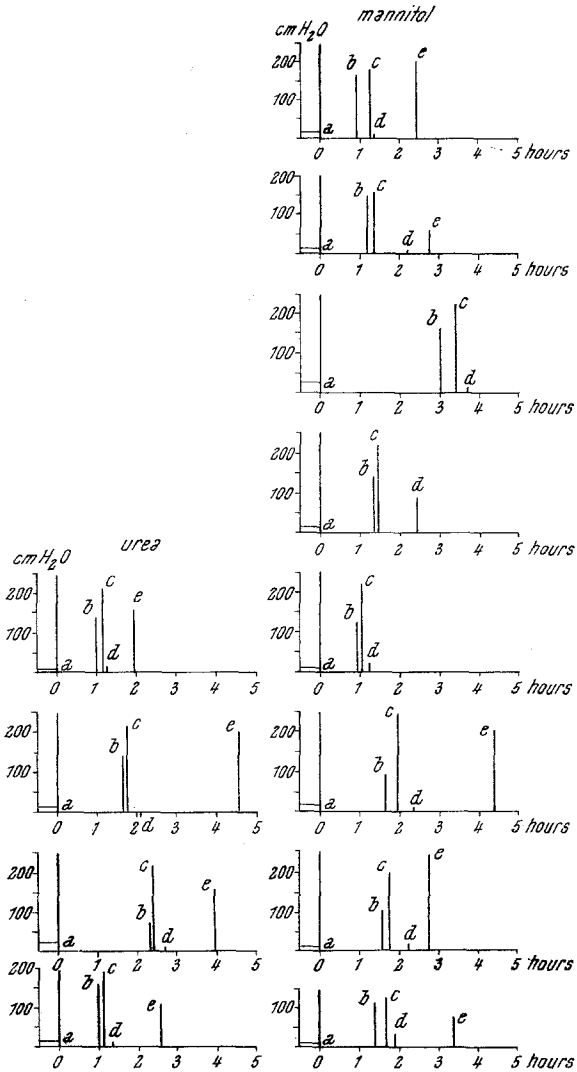

Fig. 4. *a* Initial value of intraventricular pressure, *b* indicates time of onset of respiratory disturbances and the intraventricular pressure recorded at that moment, *c* indicates respiratory failure and the intraventricular pressure at that moment, *d* the lowest intraventricular pressure recorded following administration of urea or mannitol, *e* indicates the second episode of respiratory failure and the accompanying intraventricular pressure.

Results

Although our series is too small and shows too marked individual differences to warrant definite conclusions, a few preliminary results may be presented.

We noted that the initial values of intraventricular pressure showed considerable individual variation, ranging from 40 to 300 mm H_2O with an average of 116 mm H_2O.

We found no correlation between the initial values of intraventricular pressure and the value attained upon compression of the brain stem, nor any correlation between the intraventricular pressure when respiratory

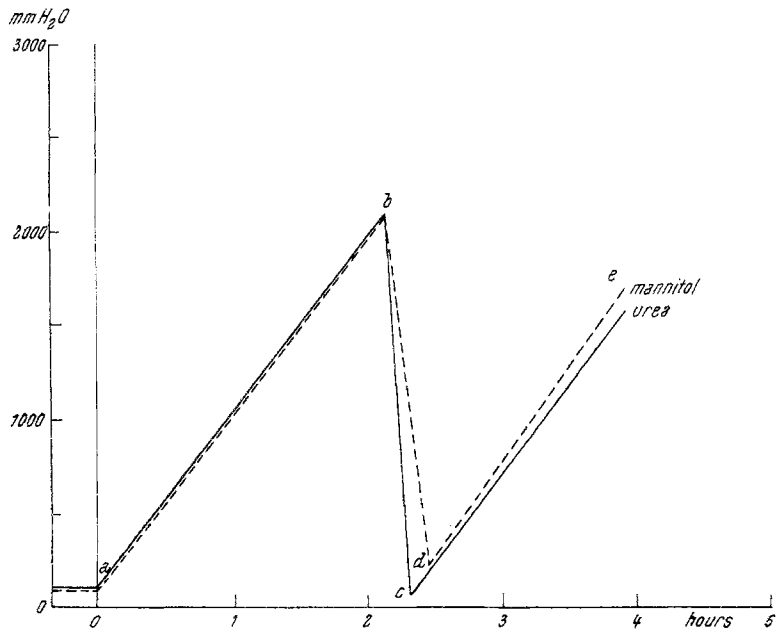

Fig. 5. Average course of intraventricular pressure after administration of urea and mannitol. *a* Initial value of intraventricular pressure, *b* the intraventricular pressure at the moment of respiratory failure, *c* lowest value of intraventricular pressure following administration of urea, *d* lowest value of intraventricular pressure following administration of mannitol, *e* the intraventricular pressure at the moment of the second episode of respiratory failure.

changes first developed and the pressure recorded at the moment of respiratory arrest.

We observed a marked decrease in intraventricular pressure both after hypertonic urea solution and after hypertonic mannitol solution.

No correlation was found between the initial intraventricular pressure, the pressure at respiratory arrest and the lowest intraventricular pressure after administration of a hypertonic solution (Fig. 3; Fig. 4).

The interval between cooling and respiratory arrest likewise varied widely, ranging from 40 to 305 minutes and averaging 125 minutes. The ease with which oedema develops ("Ödembereitschaft") possibly varies considerably from one individual to the next.

In the nine test animals given the urea solution, the intraventricular

pressure diminished within an average of 13 minutes (9–21 minutes)* to an average minimum value of 65 (12–140) mm H_2O, the average intraventricular pressure at respiratory arrest being 2050 (1250–2920) mm H_2O.

In the four animals in which a second respiratory arrest was awaited, the interval between the administration of urea and this second arrest averaged 106 (46–171) minutes. The intraventricular pressure at the second arrest was 1550 (1060–2000) mm H_2O, i. e. considerably below the value at the first respiratory arrest. After administration of urea, the interval until spontaneous respiration was resumed averaged 6 (4–25) minutes.

Thirteen animals received mannitol in the abovementioned dosage 1 minute after the occurrence of respiratory arrest, after which the intraventricular pressure diminished within an average of 22 (7–60) minutes to an average minimum of 176 (40–850) mm H_2O. In this series, the intraventricular pressure at respiratory arrest averaged 2130 (1250–2920) mm H_2O. Five of these animals were sacrificed when the intraventricular pressure attained its minimum. In the other 8 cases, a second arrest was awaited. In 3 instances, however, administration of mannitol failed to restore respiration, so that the experiment had to be ended.

In the 5 cases in which respiration could be restored, the interval until spontaneous breathing was resumed averaged 10 (5–16) minutes. In these animals the interval between the first and the second respiratory arrest averaged 106 (36–153) minutes. The accompanying intraventricular pressure averaged 1580 (650–2400) mm H_2O.

Summary and Conclusions

In 22 cats in which cerebral oedema had been produced by means of a cold-induced lesion, changes in intraventricular CSF pressure were measured after the intravenous injection of either hypertonic urea solution or hypertonic mannitol solution.

The response of the various test animals to infliction of the cold-induced lesion differed considerably between individuals, both in intensity and in course. The animals differed widely both in their initial intraventricular pressure and in the intraventricular pressure at the moment of respiratory arrest.

The increased intraventricular pressure was diminished more rapidly and more profoundly after administration of hypertonic urea solution than after administration of a corresponding amount of mannitol. Unlike *McQueen* and *Jeanes*, we found that urea and mannitol did not differ in the average duration for which they decreased intraventricular pressure (Fig. 5).

It must be pointed out that, after administration of mannitol, it was in some instances impossible to reverse the respiratory arrest which had resulted from compression of the brain stem; after administration of a hypertonic urea solution no such failures occurred. Spontaneous respiration was resumed more quickly after urea than after mannitol administration.

* Figures in brackets indicate the range.

Acknowledgement

We are much obliged to Messrs. *Flanderijn*, *Kok*, *Nagel*, and *Slauerhoff* for their technical assistance.

We also gratefully record that thus work was carried out partly on behalf of the working party for experimental neurosurgery at Groningen.

Zusammenfassung

Bei 22 Katzen, bei denen durch lokale Kälteeinwirkung ein Hirnödem erzeugt worden war, wurden die Veränderungen des intraventrikulären Liquordruckes sowohl nach intravenöser Injektion von hypertonischer Harnstofflösung als auch von hypertonischer Mannitollösung gemessen.

Die Reaktion der verschiedenen Versuchstiere auf die zerebrale Kälteläsion variierte nach Intensität und Verlauf erheblich von Tier zu Tier. Sowohl der anfängliche intraventrikuläre Druck als auch der intraventrikuläre Druck im Moment des Atemstillstandes waren bei den Tieren sehr unterschiedlich.

Der erhöhte intraventrikuläre Druck sank rascher und tiefer nach Gabe von hypertonischer Harnstofflösung als nach Gabe einer entsprechenden Menge von Mannitol. Anders als bei *McQueen* und *Jeanes* ergaben unsere Befunde, daß Harnstoff und Mannitol sich nicht hinsichtlich der durchschnittlichen Dauer der intraventrikulären Drucksenkung unterschieden.

Es muß darauf hingewiesen werden, daß es nach Gabe von Mannitol in einigen Fällen nicht möglich war, den Atemstillstand zu beheben, der als Folge einer Kompression des Hirnstammes aufgetreten war. Nach Gabe von hypertonischer Harnstofflösung kam solch ein Versagen niemals vor. Die Spontanatmung stellte sich unter Harnstoff-Therapie rascher wieder ein als unter Mannitol-Therapie.

Résumé

Chez 22 chats à qui on a provoqué un oedème cérébral au moyen d'une lésion occasionnée par le froid, des changements dans la pression intraventriculaire sont mesurés après une piqûre intraveineuse soit d'une solution hypertonique d'urée, soit d'une solution hypertonique de mannitol.

La réaction des différents animaux expérimentaux à la lésion provoquée par le froid, varie considérablement d'une individu à l'autre, à la fois en intensité et en étendue. Chez ces animaux, il y a une grande différence à la fois dans leur pression intraventriculaire initiale, et dans leur pression intraventriculaire au moment de l'arrêt de la respiration.

La pression intraventriculaire ainsi augmentée, diminue plus rapidement et davantage après l'injection d'une solution hypertonique d'urée, qu'après l'injection de la dose correspondante de mannitol. Contrairement aux résultats de *McQueen* et *Jeanes*, nous trouvons que l'urée et le mannitol ne diffèrent pas dans la durée moyenne pendant laquelle ils diminuent la pression intraventriculaire (Fig. 5).

Il faut remarquer qu'après l'administration du mannitol, il est impossible dans certains cas de faire reprendre la respiration après l'arrêt résultant de la compression du tronc cérébral ; il ne se produit aucune défaillance de ce genre après l'administration d'une solution hypertonique d'urée. La respiration spontanée se rétablit plus rapidement après l'administration de l'urée qu'après celle du mannitol.

Riassunto

Su 24 gatti, nei quali era stato provocato un edema cerebrale mediante una lesione indotta col freddo, si procedette alla rilevazione delle variazioni della pressione intraventricolare, dopo iniezione endovenosa di una soluzione ipertonica di urea o di mannitolo.

Le reazioni dei vari animali da esperimento sottoposti alle lesioni indotte da freddo differiscono da un sogetto all'altro considerevolmente tanto per il grado, quanto per il decorso. Gli animali differiscono notevolmente già nella loro pressione intraventricolare iniziale, nonchè nella stessa pressione al momento dell'arresto respiratorio.

L'aumentata pressione intraventricolare venne ridotta più rapidamente ed in maggior grado dalla somministrazione di urea, che da una corrispondente dose di mannitolo.

A differenca da *McQueen* e *Jeanes,* gli AA. riscontrarono che l'urea ed il mannitolo non differiscono nella durata media della loro azione riducente la pressione intraventricolare (Fig. 5).

Va rilevato che, per effetto della somministrazione del mannitolo, in alcuni casi fu impossibile annulare l'arresto respiratorio, dipendente dalla compressione del sistema cerebrale, mentre non si ebbe alcun caso del genere in seguito a somministrazione di soluzione di urea.

La respirazione spontanea si riattivava più rapidamente nei casi di somministrazione dell'urea, che in quelli del mannitolo.

Resumen

Se provoca un edema cerebral en 22 gatos, por medio de lesiones ocasionadas por el frío, y después de una inyección intravenosa bien de una solución hipertónica de urea ó de una solución hipertónica de manitol se miden los cambios de la presión intraventricular.

La reacción de los diferentes animales de experimentación a las lesiones provocadas por el frío varia considerablemente de unos a otros, tanto en intensidad como en extensión. En estos animales hay una gran diferencia entre su presión intraventricular inicial y entre su presión intraventricular en el momento de la parada respiratoria.

La presión intraventricular aumentada de este modo disminuye más y con mayor rapidez después de la inyección de una solución hipertónica de urea que con la inyección de la dosis correspondiente de manitol. Contrariamente a los resultados de *McQueen* y *Jeanes,* encontramos que la urea y manitol no se diferencian en su duración media, durante la cual disminuyen la presión intraventricular (Fig. 5).

Hay que destacar el hecho que después de la administración de manitol, en algunos casos, es imposible recuperar la respiración después de la parada resultante de la compresión del tronco cerebral; sin embargo, no se produce ningún fallo de este tipo después de la administración de una solución hipertónica de urea. La respiración espontánea se restablece más rápidamente después de la administración de urea que de la de manitol.

References

Beks, J. W. F., C. A. ter Weeme, E. J. Ebels, W. G. Walter, and *J. S. Wassenaar,* Increase in intraventricular pressure on cold induced cerebral oedema. Acta Physiol. Pharmacol. Neerl. *13* (1965), 317—329. — *Bering,*

E. A., and *N. Avman*, The use of hypertonic urea solutions in hypothermia. An experimental study. J. Neurosurg. *17* (1960), 1073—1081. — *Buckell, M.*, Blood changes on intravenous administration of mannitol or urea for reduction of intracranial pressure in neurosurgical patients. Clin. Sci. *27* (1964), 223—227. — *Fisher, R. G.*, Discussion of Hayes and Slocum. J. Neurosurg. *19* (1962), 69—70. — *Freemonth-Smith, F.*, and *M. S. Forbes*, Intraocular and intracranial pressure. An experimental study. A. M. A. Arch. Neurol. Psychiat. *18* (1927), 550—564. — *Javid, M. L.*, and *P. Settlage*, Effect of urea on cerebrospinal fluid pressure in human subjects. Preliminary report. J. A. M. A. *160* (1956), 943—949. — *Langfitt, T. W.*, Possible mechanisms of action of hypertonic urea in reducing intracranial pressure. Neurology (Minneap.) *11* (1961), 196—209. — *Mason, M. S.*, and *J. Raaf*, Physiological alterations and clinical effects of urea-induced diuresis. J. Neurosurg. *18* (1961), 645—653. — *Shenkin, H. A., B. Goluboff*, and *H. Haft*, The use of mannitol for reduction of intracranial pressure in intracranial surgery. J. Neurosurg. *19* (1962), 897—901. — *Smythe, L., G. Smythe*, and *P. Settlage*, The effect of intravenous urea on cerebrospinal fluid pressure in monkeys. J. Neuropath. Exp. Neurol. *9* (1950), 438—442. — *Stevenson, G. C., R. C. Jacobs, M. W. Ross, W. F. Collins*, and *C. T. Randt*, Effect of urea on central nervous system activity in the cat. Amer. J. Physiol. *197* (1959), 141—144. — *Stubbs, J.*, and *J. Pennybacker*, Reduction of intracranial pressure with hypertonic urea. Lancet *1* (1960), 1094—1097. — *Wise, B. L.*, and *N. Chater*, The value of hypertonic mannitol solution in decreasing brain mass and lowering cerebrospinal-fluid pressure. J. Neurosurg. *19* (1962), 1038—1043.