Studies on the Formation and Absorption of Cerebrospinal Fluid in Experimental Cerebral Edema and the Effect of Hypertonic Urea on the Cerebrospinal Fluid Circulation

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INTRODUCTION

Attention has been attracted recently to the pathological physiology of cerebral edema or swelling. Differentiation of these latter two terms has so far been made according to the site in which fluid accumulates within the brain tissue. Namely, extracellular distention by hyperhydration in brain parenchyma has been called as cerebral edema, and intracellular distension by hyperhydration has been mentioned as cerebral swelling.[44)45)] However, the consensus is that they represent variable degrees of the same process on the basis of recent development of the electron microscopic study.[20)31)33)34)36)43)51)52)] And it now appears best to consider them synonymous, rather than by application of different names. Severity of the pathological process should be related to degree of alteration.

Cerebral edema is observed typically in man in the tissue adjacent to a tumor as well as contused brain tissue subsequent to a trauma. Experimentally it may be produced by inflating an extradural balloon.[28)29)] Production of experimental cerebral edema by intracarotid injection of salad oil has also been reported.[23)]

Since the management of cerebral edema is a key point in the treatment of postoperative or posttraumatic patient in the field of Neurosurgery, enormous efforts has been exerted to elucidate this pathological condition experimentally or clinically, mainly on the morphological basis.

In spite of extensive works on this subject, problem of the dynamics of cerebrospinal fluid (CSF) circulation under cerebral edema has remained unsolved. Considering that changes in the CSF space, in association with that of intracranial vascular space, are involved in the essential mechanism of the increase in brain bulk, to make clear the changes in the formation and absorption of CSF within the edematous brain is to be a matter of interest.

On the other hand, it has been known that intravenous hypertonic solutions well reduce the brain bulk.[30)47)] Hypertonic urea is now widely used as an effective cerebral hypotensor in the field of neurology and neurosurgery.

In 1962, Pappenheimer and his collaborators[38] reported the method for measuring accurately the formation and absorption of CSF in goats, using a technique of ventriculo-cisternal perfusion with artificial CSF containing inulin. Davson and Pollay[13][14] applicated this technique to rabbits and studied the absorption of some substances from the CSF.

In this study, the cerebral ventricular system was perfused according to the method described by Davson[39] in order to estimate the rates of formation and absorption of CSF under the condition of cerebral edema. The effect of intravenous hypertonic urea on the production and absorption of CSF in this pathological condition was also studied.

METHOD

Animals and Anesthesia. Albino rabbits, weighing between 1.9 and 3.2 kg, were used for the study. Anesthesia was induced with 15 mg/kg of intravenous sodium pentobarbiturate, and maintained with additional injections of small dose during the experimental period. Artificial respiration was applied by a positive-negative animal respirator connected to the intratracheal tube. Respirator was adjusted to 800 cc/min. of total exchange volume at the rate of 32/min. The head of rabbit was then fixed to a stereotaxic instrument.

Surgical Technique. Insertion of the inflow and outflow cannulae was performed according to the description by Pollay and Davson[39] with some modification.

On the surgically exposed parietal bone a twist drill hole was made at the point of 10 mm. lateral from the midline. Through this hole, 21 gauge blunt-tipped needle connecting with the fine polyethylene tube was driven into the lateral ventricle with use of a micromanipulater. Attainment of correct placing of the tip of a needle was estimated by a rapid drop in pressure in the inflow tubing. Insertion of the outflow drainage tube into the cisterna magna was made by introduction of the tip of a polyethylene tube, 0.9 mm. in internal diameter, through the puncture hole in the exposed membrane covering the cisterna magna by midline dissection of the nucal musclature.

Ventriculo-cisternal perfusion. Entire perfusion system is diagramatically shownin Fig. 1. Polyethylene tubing from the inflow cannula was connected to the 20 ml. injection syringe filled with artificial CSF containing (mM) : NaCl 154, KCl 2.8, CaCl 1.1, $MgSO_4$ 0.8 and inulin (80mM/100ml). The proportion of the cations are those found in the cerebrospinal fluid of rabbits according to Bradbury and Davson.[9] Driving of the syringe was established with the constant speed slow injection machine (Nakagawa Seikodo). Collection of fluid from the cisterna magna was carried out under a controlled negative pressure

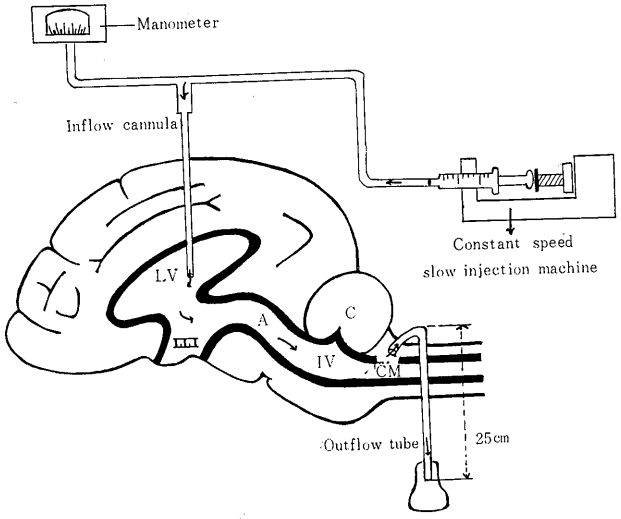

Fig. 1. Diagramatic representation of experimental perfusion system. The inflow cannulae is inserted into the lateral ventricle and outflow tube is put in the major cistenra.
A, indicates aqueduct; C, cerebellum; LV, lateral ventricle; MC, major cistern; III, third ventricle; IV, fourth ventricle.

of 25 cm H_2O. Empty sampling tubes were weighed prior to the experiment. The rate of perfusion was approximately 46 μl/min. and the exact rate was determined at the end of each experiment by weighing the effluent from the inflow tubing during a ten minute period. This rate was found to vary between 44 μl and 46 μl/min.. The outflow orifice was generally placed 25 cm. beneath the external auditory meatus. However, adjustment of outflow pressure was sometimes necessary in order to correct irregularities or stoppage of flow. At ten-minute intervals the tube plus sample was weighed and sealed with Parafilm for subsequent analysis. Duration of the experiments varied between two and three hours. After the first thirty minutes of the perfusion, the rate of outflow from the experimental system became reasonablly steady. Attention was paid to avoid any leak around either the inflow cannula or the outflow tube. Perfusion with dye solution was performed after each experiment, and if any leak was disclosed, samples obtained were discarded.

Determination of Inulin. Inulin was determined by the resorcinol method of Hubbard & Loomis (1942).[26] A spectrophotometer (Hitachi-Parkin Elmer, Type 139) was used for the analysis at the wave length of 450 mμ.

Gas analysis of arterial blood. In order to eliminate tha factor of gas metabolism, changes of which seemed to affect the rate of formation and absorption of CSF, pCO_2, pO_2 and pH were measured in each experiment. The measurment of pCO_2, pO_2 and pH were made with I.L. meter (I.L. Co., U.S.A. model 113-S2.)

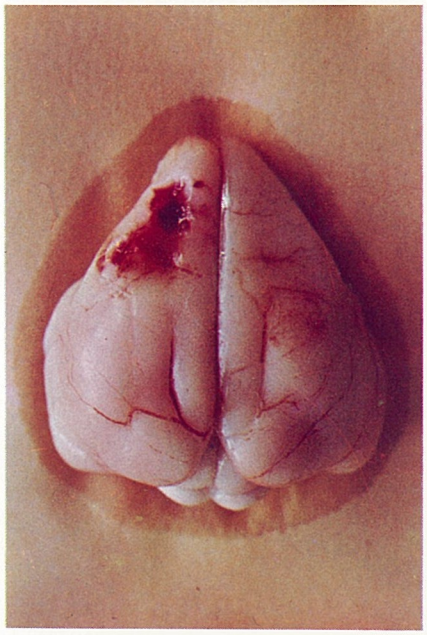

Fig. 2. Macroscopic appearance of the rabbit's brain which was taken out 24 hours after deflation of the balloon. In the compressed hemisphere, marked flattening of the cerebral gyri is seen.

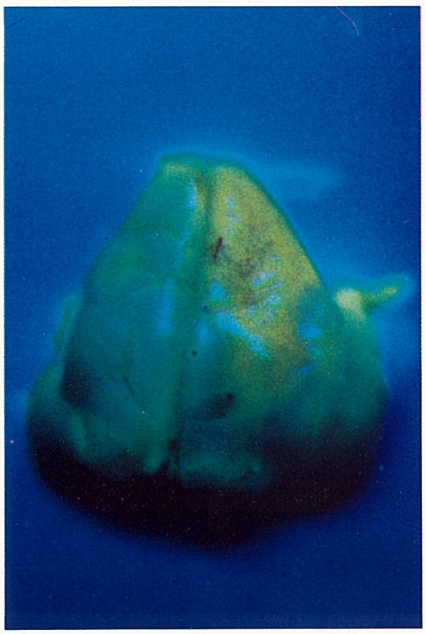

Fig. 3. Edematous brain (by the compression method) which have been injected with 20 % fluorescein via the carotid artery shows a fluorescent under ultraviolet light.

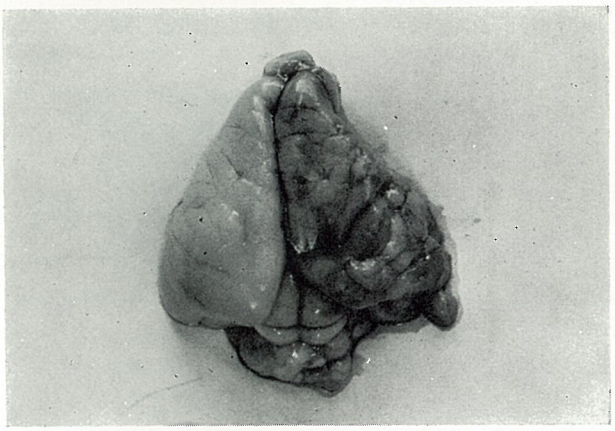

Fig. 4. The brain following the injection of sesame oil from the right carotid artery shows a marked staining with dye in the hemisphere of the injected side. The dye had been systemically injected prior to the oil injection.

Method of producing cerebral edema in animal.

1. *Extradural balloon method by Ishii.*[28] A small burr hole, 7 mm. in dimeter, was trephined on the parietal skull of anesthetized rabbit. The dura mater was stripped away from the skull as widely as possible through the burr hole. An empty condom balloon with an attached polyethylene tube was inserted into the extradural space toward the frontal region. After plugging the burr hole with bone wax, the wound was sutured. Surgical procedures were done under strictly sterile precautions. The polyethylene tube protruding the incision was then connected to a syringe with saline. With aid of the constant speed slow injector above mentioned, the balloon was slowly filled with saline. Total amount of saline introduced into the balloon was approximately 1.5 ml. which required the interval of injection for about 90 minutes.

After 24 hour period of compression, contents of the balloon were evacuated. Approximately 1/3 of the animals died following various neurological symptoms within 24 hours after the inflation of the balloon.

Another 24 hours were allowed to wait before the ventriculo-cisternal perfusion since the most conspicuous change of the whith matter due to cerebral swelling took place at this stage according to Ishii et al.[28]

2. *Intracarotid sesame oil injection by Hatanaka.*[23] Sterile sesame oil, 0.2 ml/kg body weight, was injected from the surgically exposed bilateral carotid arteries in anesthetized rabbit.

The effect for producing cerebral edema by either method was found to be quite consistent. Macroscopically, the specimen of the brain subjected such treatment looked as watery, and cerebral gyri were appeared to be flattened (Fig. 2).

To examine whether cerebral edema occured within the specimen, following methods were employed: 20 % sodium fluorescein was injected intravenously immediately before sacrificing animals. The entire brain was then removed as quickly as possible.

Observing the brain under a ultraviolet light, yellowish green fluorescein was given out over the cortical surface if the brain was edematous, since the fact that this material, which normally does not cross the blood-brain barrier, could move in tissue penetrating the disrupted barrier when cerebral edema is present. This serves to the indication of the cerebral edema or swelling. Severe cerebral edema produced by the extradural balloon method is well illustrated in Fig. 3.

Another method to examine the occurrence of cerebral edema is dye technique. The principle of this technique is as same as the fluorescein method; in the condition of cerebral edema, disrupted blood-brain barrier permits to penetrate dye stuff into the cerebral tissue from circulating blood.

Fig. 4 shows the staining of the hemisphere on which side intracarotid sesame oil injection has been carried out.

RESULTS

Rate of the formation and absorption of cerebrospinal fluid in normal rabbits.

The inflow rate of perfusion fluid ($\dot{V}i$) varied between 44 μl/min. and 46 μl/min.. The average rate of for all the perfusion experiments was 45.8 μl $\pm$ 0.8 μl/min.. The outflow rate ($\dot{V}o$) varied considerably time to time. Theoretically, the outflow would exceeds inflow rate if there were no bulk absorption of the fluid. Practically, however, the outflow rate sometimes appeared to be less than the inflow rate.

Formation rate of CSF was calculated by the method of Heisey et al. [24] according to the following principle. It is assumed that, because of its high molecular weight, inulin does not diffuse across the ependymal lining of the ventricular system, so that almost all inulin lost from CSF can be accounted for bulk absorption distal to the fourth ventricle. Therefore, the clearance of inulin virtually represente the rate of bulk absorption.

From above idea, the rate of the formation of CSF ($\dot{V}f$) was expressed by the sum of inulin clearance (C_{IN}) and outflow-inflow difference ($\dot{V}o - \dot{V}i$) which involved both formation and absorption.

i.e., $\dot{V}f = C_{IN} + \dot{V}o - \dot{V}i$

The clearance of inulin was calculated from the known concentration of inulin in the influent (ci) and measured concentration of this material in effluent (co)

i.e., $C_{IN} = \dfrac{\dot{V}ici - \dot{V}oco}{co}$

It was demonstrated that the outflow-inflow difference was a simple function of hydrostatic pressure, while the rate of formation was independent of the hydrostatic pressure within the physiological range. [24]

After setting up the perfusion, two samples of the effluent were discarded since reasonable steady-state was reached within the first 30 minutes of perfusion.

Concering the rate of formation calculated by above equations showed considerable fluctuation in each sample. Theyvaried from 10.3 to 24.7 μl/min. Average value of 8 experiments varied from 10.6 to 22.0 μl/min.; 18.0 $\pm$ 2.8 (S.D.) μl/min. in average.

The rate of bulk absorption was measurea as clearance of inulin, as mentioned above. Variation of the calculated data was from 7.6 μl/min. to 26.6 μl/min. in each sample. Average value of 8 animals varied from 11.0 to 15.0 μl/min,; 13.2 $\pm$ 2.7 (S.D.) μl/min. in average. (Table 1)

Rate of the formation and absorption of cerebrospinal fiuid in cerebral edema.

In the group of extradural balloon method consisted of 6 animals, showed a highly significant decrease in both the rate of formation and absorption as compared with the controls. Average values were calculated as 14.0 $\pm$ 2.4 μl/min. in formation rate and 9.6 $\pm$ 2.5 μl/min. in absorption rate.

Table 1.
Mean rate of formation and absorption of CSF

Group			Rate of CSF Formation (μl/min.)	Rate of CSF Absorption (μl/min.)
Control		(8)	18.0 ± 2.8	13.2 ± 2.7
Cerebral Edema	Extradural Balloon	(6)	14.6 ± 2.4 *	9.9 ± 2.5 *
	Sesame Oil Injection	(6)	17.5 ± 4.9	9.8 ± 4.1 **

*P<0.05 **P<0.1
Numbers of experimental animals are shown in parentheses.
Numerals are expressed by mean values with standard deviations.

The second group of cerebral edema ; carotid injection of sesame oil, on the other hand, the rate of formation failed to show a significant change from the control (17.5 ± 4.9 μl/min.), while absorption decreased significantly (9.8 ± 4.1 μl/min.)

Effect of hypertonic urea on the formation and absorption of cerebrospinal fluid.

Normal animals. Average rate of the formation of CSF afterintravenous administration of 30 % urea was calculated as 18.3 ± 2.3 μl/min. in 5 animals. This rate was quite comparable with the control value without urea (18.0 μl/min.), while the rate of absorption was significantly increased to 18.8 ± 2.5 μl/min. in average, as compared to the controls (13.2 μl/min.). (Table 2)

Table 2.
The effect of Urea on the formation and absorption of CSF

Group			Rate of CSF Formation (μ/1min.)	Rate of CSF Absorption (μl/min.)
Control		(8)	18.0 ± 2.8	13.2 ± 2.7
Urea Inj.	Without Cerebral Edema	(5)	18.3 ± 2.3	18.8 ± 2.5 *
	Cerebral Edema	(5)	13.6 ± 2.1	14.0 ± 2.3 *

*P<0.05
Numerals are expressed by mean valueswith standard deviations.
Numbers of experimental animals are shown in parentheses.

Curves of formation and absorption rates in each time interval along the course of the experiment after steady state was attained were shown in Fig. 5 & 6. The increased rate of bulk absorption was maintained during an hour following the injection of urea as shown in Fig. 6.

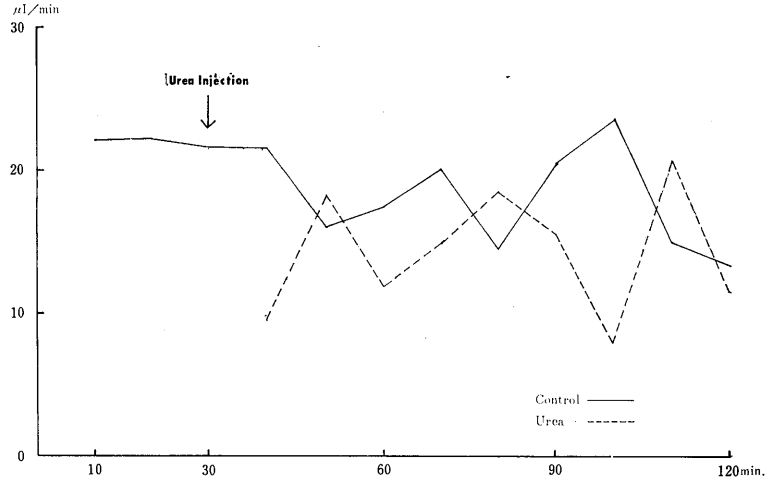

Fig. 5. The effect of Urea on the bulk formation of cerebrospinal fluid in the normal rabbits

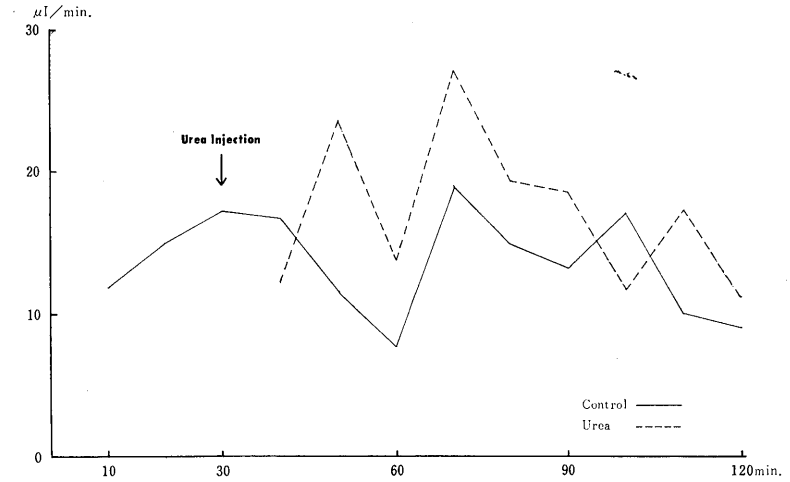

Fig. 6. The effect of Urea on the bulk absorption of cerebrospinal fluid in the normal rabbits

Animals with cerebral edema. (Extradural balloon method). In the presence of cerebral edema, average rate of formation of CSF under intravenous administration of hypertonic urea was calculated as 13.6 ± 2.1 μl/min. in 5 animals. This value was comparable with that of the extradural balloon group without urea (14.6 μl/min.), and significantly lower than that of the normal animals with urea (18.3 μl/min.).

The rate of absorption was calculated as 14.0 ± 2.3 μl/min. in average, which was significantly higher than that of the extradural balloon group without urea (9.6 μl/min.), but lower than that of normal animals with urea (18.8 μl/min.).

The changes of these values were traced along the experimental course in Fig. 7 & 8. The latter figure apparently indicates the difference of the effect of urea on the absorption rates throughout the course of perfusion between two groups with or without cerebral edema.

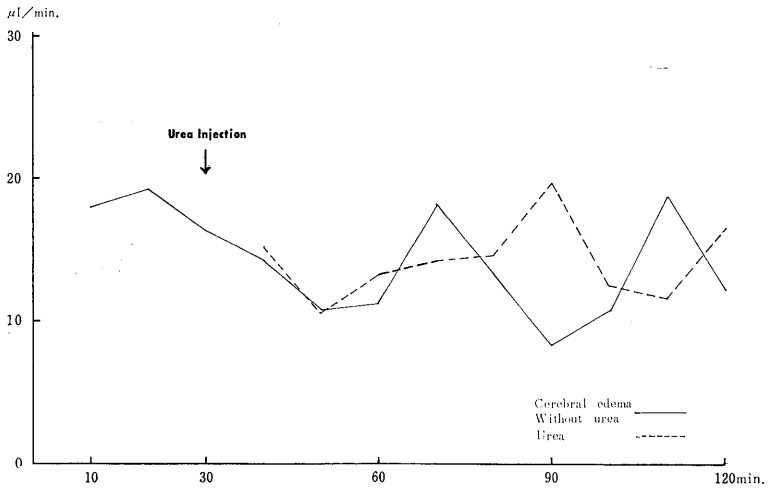

Fig. 7. The effect of Urea on the bulk formation of cerebrospinal fluid in rabbits with cerebral edema

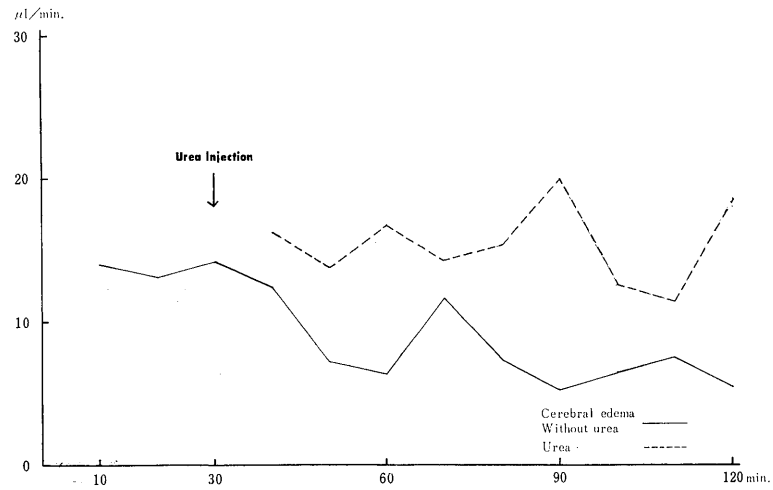

Fig. 8. The effect of Urea on the bulk absorption of cerebrospinal fluid in rabbits with cerebral edema

Gas analysis of blood during the course of the experiments.

Changes in arterial pCO_2, pO_2 and pH during the course of the experiment were summarized in Table 3. Slight increase of pCO_2 in both groups of control and cerebral edema and slight increase of pH in cerebral edema group were observed. Therfore slight tendency to respiratory alkalosis was resulted probably from artificial respiration.

Table 3.
pCO_2, pO_2 and pH in arterial blood during perfusion

		before 10 min.	after 20 min.	50 min.	80 min.	110 min.
Control	pCO_2 (mmHg)	41.6	36.4	34.8	34.0	32.3
	pO_2 (mmHg)	74.0	76.5	75.0	75.2	75.1
	pH	7.400	7.350	7.371	7.420	7.475
Cerebral Edema	pCO_2 (mmHg)	42.0	37.0	35.2	36.5	32.0
	pO_2 (mmHg)	73.0	77.0	75.0	74.0	75.0
	pH	7.380	7.342	7.475	7.475	7.500

DISCUSSION

In the clinical observations, cerebral edema is frequently encountered following evacuation of the intracranial space occupying lesion. Experimentally produced cerebral edema by the technique of extradural compression was designed to simulate such clinical condition.

Microscopic studies by Ishii et al.[28] revealed that the most conspicuous increase in the interstitial tissue fluid was seen in the specimens of the brain of cats sacrificed 24 hours after deflation of extradural balloon which had been compressing the brain for a period of 24 hours. In this stage, they described, gross appearance of the brain was characterized by an increase in size of the affected hemisphere, particularly of the white matter with reduction of the ventricular size and distortion of the ventricular shape. Histologically, alveolar or sieve-like appearance of the tissue, showing a typical "spongy appearance" stage of brain swelling was observed.

Stern[49] also employed this technique for the production of experimental cerebral swelling in cats. His experimental animals underwent 30 minutes of brain compression and were observed for period up to 60 minutes after the

balloon was released. Consequently, he observed the secondary rise in CSF pressure which might be indicative of postcompression swelling 4 of 12 animals. He found, however, that the brain mass increased in content of water only minimally but not enough to account for the marked rise in CSF pressure while the CSF volume increased significantly. This might appear to be resulted from the osmotic pressure of solutes released from brain cells and solutes crossing the injured blood-brain barrier.

Pathology of the brain following carotid injection with oil is to be compared with that in fat embolism. Blackwood[7] stated that in patients who die within the first 3 or 4 days the white matter of the brain is diffusely studded with petechial hemorrhages and microscopically these are pericapillary, ring and ball hemorrhages. Numerous fat globules are visible in these capillaries. Sometimes the capillary walls show focal necrosis. In contrast to the grey matter, capillaries in the white matter are long, anastomoses are few, so that the wall of the blocked capillary is rendered anoxic; the endothelial cells less firmaly bound together, or die, and erythrocytes and plasma leak out. Such diffuse tissue anoxia leading to ischemic necrosis causes cerebral edema.

Once the fluid has left the vessels, whatever the cause may be, it will tend to diffuse. From the experimental evidence by Bertrand,[6] in cerebral edema, exessive fluid leaked from the capillaries close to the causative lesion may diffuse widely towards the absorbing veins and venules, which found in the walls of the ventricles, at the periphery of the white matter and in the grey matter itself.

In animal experiments Bering[4] found that cerebral and cerebellar grey matter were in D_2O equilibrium with blood, following intravenous administration, within a minute of injection.

From these findings, together with those of Sweet et al[50] in human subjects, it is apparent that water exchanges freely across all membranes and lining epithelia throughout the fluid system, i.e., there is no blood-brain or blood-CSF barrier to water.

On the other hand, in experimental cerebral edema produced by the intravenous infusion distilled water, Rosomoff[43] found a fourfold increase in CSF pressure after 30 minutes of infusion. The rise in pressure, he concluded, resulted from a 2.5 % increase in brain water. And compensation for the increase in brain water was achieved by a reduction in both the CSF and intracranial blood volumes.

There is a discrepancy between these results and Stern's observation which mentioned above, as far as the volume of CSF in cerebral edema is concerned.

Neverthless, in the present study, calculated rates of the formation and absorption of CSF in cerebral edema appeared to show greater decrease in the latter than in the former in comparison with normal animals; 17.8 % decrease

in the formation rate and 27.2 % decrease in the absorption rate in extradural balloon group, while no significant changes in the formation rate and 25.7 % decrease in the absorption rate in sesame oil injection.

These results suggest that CSF volume tendes to increase in such pathological situation. However, such assumption may not always accurate because such factor as the effect of hydrostatic pressure on the bulk absorption and loss of the fluid by diffusion within the ventricles were not taking into account.

Higashi and Kokura,[25] in our department, previously studied the dynamics of CSF using radioactive phosphate in rabbits under the condition of acute stage of brain compression and 24 hours after the insufflation of extradural balloon. They also reported the considerable decrease in ^{32}P turnover rate either from blood to CSF or reverse direction in both immediately after or 24 hours after the compression.

Therefore, it is surmised that both formation and absorption of CSF decreased in every stage of cerebral edema from a quite initial pariod, probably no edema in the cerebral tissues but acutely elevated CSF pressure in this stage, to the maximal stage of cerebral edema.

In fact, importance will exist not in assuming the volume of CSF but in estimation the dynamics of CSF circulation in such particular situation of the brain.

The experimental evidence that cerebral edema gives rise to a reduction of cerebral blood flow[27] is enough to account for the decrease in the formation rate of CSF under such condition, though it failed to be demonstrated in a group of sesame oil injection in the present study. However, a decrease in bulk absorption rate in this pathological condition is difficult to explainon the basis of the elevated CSF pressure. Heisey et al[24] indicated that inulin clearance increased linearly with hydrostatic pressure at pressure above -15 cm. H_2O. Therefore, some of other factors which are responsible to the inhibition of the bulk absorption than the pressure might exist such as compression to the subarachnoid pathways or congestion in cerebral venous system and so on.

Furthermore, respiratory acidosis was proved to increase the production rate to CSF from the choroid plexus.[1] In the present study, however, blood tended to alkalosis which might be too slight to influence the formation of CSF in both normal and edema groups.

The earliest attempt at measuring the rate of formation of the CSF consisted in simply allowing or to drain from the inserted cannula into the cisterna magna or the aqueduct on Sylvius in animals.[11][19][22][40]

Various tracers including radioisotopes have been used as a measure of the rate of formation or absorption of CSF.[4][11][25][50] The rate of formation or absorption of the fluid was estimated by the rate of turnover of these tracers between blood and CSF. However, these observations beg question as to the

relationship between turnover of each tracer and turnover of fluid as a whole. In this connection, application of the tracer study in this complicated physiological system regardless of such intricate factors as lipoid solubility or affinity to the cerebral tissues of each tracer, tends to make an error in interpretation.

Since the quantitative measurement of the formation and absorption of CSF was made with the technique of ventriculocisternal perfusion in goats by Pappenheimer et al,[38] the technique has been applied to the CSF flow study in other species such as cats,[13][21] rabbits,[9][13][14][39] dogs[5][37] and rats[11] with varied experimental conditions. These studies have brought a great contribution in the field of physiology of CSF.

On the other hand, since the studies of weed and McKibben,[53][54] the effect of intravascular hypertonic solutions on dehydration of the central nervous system has been well known. The demonstrations that the intravenously administered hypertonic urea profoundly lowered the intracranial pressure by Smyth and others[47] in monkeys and by Javid and Settlage[30] in human subjects proceeded the clinical use of this stuff.

Previous observations with ^{32}P by Higashi and Kokura,[25] pronounced facilitatory effect of urea upon the CSF absorption (turnover rate of ^{32}P from CSF to blood) was confirmed in either normal rabbits or those in acute stage of brain compression, but the problem of its effect on the edematous brain has remained unsolved.

The present studies, otherwise, recomfirmed the same effect of hypertonic urea on the absorption of CSF in normal rabbits.

The rate of formation of CSF, on the other hand, was not altered in the present experiments irrespective of presence or absence of cerebral edema, though a considerable fluctuation was observed along the course of the experiment. This result is somewhat different from the previous data using ^{32}P, where the rate of turnover of ^{32}P from blood to CSF slightly increased in all series of the experiment; normal, immediately after, and 24 hours after the brain compression. This may probably mean enhanced permeability to phosphate at the blood CSF barrier, but not the hyperfunction in the CSF formation.

When hypertonic urea is given in the blood circulation, a large osmotic pressure in blood cause drawing water out of the brain. Experimental evidences revealed the apparent decrease in the size of the brain with increase of the volume of intracranial blood and CSF in such situation,[42] being compatible with the Monro-Lellie's low: in the central nervous system the total volume of blood, neuraxis, and CSF is constant in an essentially closed system.[8][55]

The present results of the dynamics of CSF under hypertonic urea, together with the previous data, coincident with above concept; i.e. the phenomena that the formation of CSF is maintained in a constant level on one hand and the absorption of it reduces considerably on the other hand was interpreted as a

decrease in the total volume of CSF in a closed system.

In the condition of cerebral edema, the situation became more complicated. The rate of formation of CSF was quite comparable with that in the same condition without urea ; i.e. no significant effect of urea was observed upon the edematous brain. On the other hand, the rate of absorption increased considerably in comparison with that of the same condition without urea, while this elevated value was far less than the increasea level in the normal control with urea.

Summarizing above results, it appears that urea again contributes to the increase in bulk absorption of CSF in the edematous brain, but not exceedes the control level in normal state. In other words, it is assumed that the same effect in draining the CSF as normal animal may be unable to expect in the edematous brain.

Current concept suggests the more harmful effect of the hypertonic solution than good in the presence of a disrupted blood-brain barrier, for they eventually would pass this barrier into the brain so as to increase edema and swelling by drawing in water. Many experimental evidences have been in favor of this concept.[3)15)34)35)48)]

In the present experiments, however, increased bulk absorption was maintained longer in the edematous brain than in the normal group. Therefore, such phenomenon that water is drawn into the edematous brain is hardly infered from such a short duration of the experiment.

Urea is reported to penetrate into the brain slowly.[46)] In the normal brain urea reaches a peak concentration in about 6 hours and then the level decreases until about 6 hours later when the blood-brain barrier equilibrium develops.

In the edematous brain, Luse and Harris[34)] demonstrated rehydration of urea induced dehydrated brain. If edema was produced after dehydration, water again went into the shrunken oligodendroglial cytoplasm, resulting in the same appearance as that seen with primary edema.

Although at what rate rehydration takes place within the edematous brain following administration of urea is not clear, rebound phenomenon may occur much more rapidly when edema exist than in the normal brain. More extensive study is required in order to elucidate such problem.

SUMMARY

The rate of bulk formation and bulk absorption of cerebrospinal fluid (CSF) was measured by means of ventriculo-cisternal perfusion with artificial CSF associated with inulin dilution technique in rabbits. The formation rate was calculated from outflow-inflow volume difference and inulin clearance, while the absorption rate was estimated by the latter.

Experiments were carried out in normal animals and those with cerebral edema. The effect of intravenous hypertonic urea was examined in each experimental group. Cerebral edema was produced by extradural balloon method and intracarotid injection of sesame oil.

The rate of formation and absorption of CSF in the normal rabbits were estimated as 18.0 ± 2.8 and 13.2 ± 2.7 μl/min. respectively.

Formation rate of CSF was decreased to 82 % of control in the extradural balloon group while no significant change in the oil injection group. On the contrally, considerable decrease in the absorption rate was observed on cerebral edema of both groups; 73 % and 74 % of controls in the balloon and oil injection groups respectively.

Hypertonic urea caused significant increase in the bulk absorption of CSF in the normal as well as edematous brain, 42 % and 46 % increase in each group, while in the latter the increment by urea was unable to recover the decrement caused by cerebral edema.

From above results, it is suggested that the efficacy of hypertonic urea on the edematous brain may be limmitted as compared with that in the normal animals.

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