

## THE CEREBROSPINAL FLUID PRODUCTION RATE IN THE EXPERIMENTALLY INDUCED EDEMATOUS BRAIN AND INFLUENCES OF DEXAMETHASONE UPON IT\*

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### ABSTRACT

Cerebral edema must be closely implicated in the cerebrospinal fluid production rate and corticosteroid, which is effective to reduce cerebral edema, must have influence upon the rates of the cerebrospinal fluid production in the edematous brain. There has been a little of previous studies which dealt with the influence of corticosteroid upon the cerebrospinal fluid production rate, but little of reports of studies of the changes of the cerebrospinal fluid production rate in the edematous brain as yet. In this series of experiments the change of the cerebrospinal fluid production rate in the experimentally induced edematous brain and the influence of dexamethasone upon it were studied in dogs by means of ventriculo-cisternal perfusion technique. The dog with his head shaken by the newly designed machine was anesthetized and the lateral ventricle and the cisterna magna were punctured 24 hours after shaking. The artificial cerebrospinal fluid containing of inulin as a tracer was pumped into the lateral ventricle of two groups of dogs with and without intravenously administered dexamethasone, and droplets out of the cisterna magna were sampled. Results by this experiment were the reduction of the cerebrospinal fluid production rate in the edematous brain and the further reduction of it in the edematous brain after the dexamethasone administration. This suggests that dexamethasone may act closely on water-ion transpot in the cerebrospinal fluid secretion system.

### INTRODUCTION

Cerebral edema is the most important problem in neurosurgery that must be solved in the near future. In recent years, many significant new discoveries have been made by the application of electron microscopy, radioactive isotopes and improved chemical determinations.

Hypertonic solutions, such as urea, mannitol and glycerol, have been used and are actually effective in order to reduce the increased intracranial pressure.

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It may be thought that mechanism of these drugs consists of withdrawal of water from the central nervous system by increasing the osmotic pressure of blood plasma. Corticosteroids have also been of great use for reducing cerebral edema by head injury or surgical attacks of intracranial tumors and aneurysms. The first observation of the effects of corticosteroids to the cerebral edema was made by Prados *et al*<sup>1)</sup> in 1945, since that a great deal of studies in order to clarify the mechanism of the actions of corticosteroids were made by many investigators, but it has not been clear as yet. There have been many studies of the cerebral edema and the actions of corticosteroids to it which were observed the changes in the cells, fibers and vessels within the gray and white matters, but little of papers with regards to the influences of corticosteroids on the cerebrospinal fluid production rate are seen. There are a few of articles reported by Francisco Garcia-Bengochea<sup>2)3)</sup> and by Osamu Sato<sup>4)</sup> who asserted the reduction of the cerebrospinal fluid production rate after the administration of corticosteroid to the normal animals. However, they did not mention the influences of this drug on the cerebrospinal fluid production rate in the edematous brain.

In view of this, it seemed that an attempt to study the relations between the cerebrospinal fluid production rate and the cerebral edema and to make clear the influences of corticosteroid on it would be of interest and might contribute to any further development of investigations in the central nervous system.

The changes of the cerebrospinal fluid production and absorption rates in the experimentally induced edematous brain were previously observed<sup>5)</sup>. In addition to it, the influences of corticosteroid upon the cerebrospinal fluid production and absorption rates in the edematous brain were experimented and discussed in this paper.

#### MATERIALS AND METHODS

##### A) *Experimental Animals and Anesthesia*

The experimental animals were the male or female mongrel dogs weighing some 15 kg. The animals were anesthetized with intraperitoneal thiobarbiturate (ISOZOL) in dosis of about 30 mg per kg of body weight. Those dogs were destined to shake their heads without the controlled respiration. To proceed the ventriculo-cisternal perfusion and to get the blood samples so as to determine the cerebral blood flow (CBF), dogs were endotracheally intubated and attached to a volume limited respirator about 200 ml of tidal volume, and given 20 mg of succinylcholine chloride intramuscularly. The respiratory rate was kept constant throughout the experiment ranging from 25 to 30 per min.

### B) Method to produce Cerebral Edema

A newly designed shaking machine was used in order to produce a diffuse brain edema of constant degree. Dogs were placed in a prone position with the head being slightly elevated and fixed at four points at bilateral maxillae and mandibles. A motor shook the dog's head back and forth for 10 minutes in frequency of 4 cycle per second with its amplitude of 6 cm. This is shown diagrammatically in Fig. 1. After shaking, dogs were intravenously administered 5% glucose solution in dosis of 50 ml per kg of body weight and left without any diet in preparation to following perfusion performed in 24 hours after their heads were shaken. The schema for head shaking is illustrated in Fig. 1.

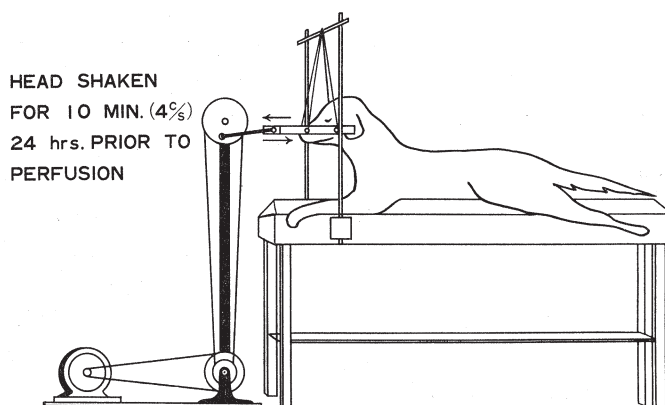


FIG. 1. Schema of head shaking.

### C) Ventriculo-Cisternal Perfusion

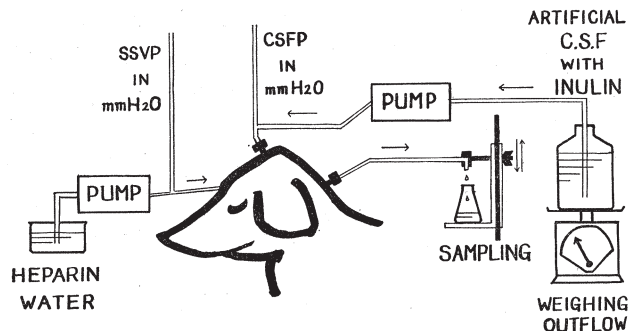
Method of ventriculo-cisternal perfusion was made after Bering and Sato<sup>6)</sup> who modified the method described by Pappenheimer *et al.*<sup>7)</sup> and by Heisey *et al.*<sup>8)</sup> Dogs, 24 hours after shaking, were anesthetized and fixed on an operating table as same as above, connected to the respirator and given 20 mg of succinylcholine chloride intramuscularly. Using a surgical technique, a 5 cm midline scalp incision extending from the frontal to the occipital region was made. Unilateral temporal muscle fibers and the periosteum, usually on the left, were reflected downwards. A small trephine to implant a No. 17 gauge needle of 1.7 cm in length with knurled round hub was made at the point of 37 mm anterior to the external occipital protuberance and 7 mm laterally from the midline. Through this needle, ventricular puncture could be made. Another trephine was made on midline just behind the frontal sinus and a Bardic 1519 catheter was canulated into the anterior portion of the superior sagittal sinus. This catheter was connected with NF-2 silicone rubber tube

through which negligible small volume of saline contained heparin solution was pumped constantly at 22 mmH<sub>2</sub>O of pressure using a Sharp Model SP-11 pump. And then a rough silk suture was made over the scalp incision. NF-2 silicone rubber tube which was 2 mm in inner diameter and 3 mm in outer diameter, was also used for inflow and outflow tubing. A No. 20 gauge needle was carefully introduced into the lateral ventricle through the No. 17 gauge guide needle which was readily implanted and secured to the skull. An inflow tube was connected to it and the perfusion fluid was sent through this tube into the ventricle from the inflow reservoir bottle by means of the pump, which was used the same as the pump for superior sagittal sinus irrigation. The pump for ventriculo-cisternal perfusion was set providing inflow rate at about 0.35 to 0.40 ml per min.

Another No. 20 gauge needle connected with the outflow tube was introduced into the cisterna magna through the foramen magnum percutaneously. The cerebrospinal fluid pressure could be altered on purpose by changing the height of the outlet of the outflow tube. Special attention was paid not to allow any leakage throughout the above mentioned procedures.

The perfusion fluid was made up to the average composition of the cerebrospinal fluid (CSF) of the dog<sup>9)</sup> and this contained 153.2 mEq/l of sodium, 122.27 mEq/l of chloride, 2.68 mEq/l of potassium, 27.95 mEq/l of HCO<sub>3</sub> and 5.87 mEq/l of HPO<sub>4</sub>. Just prior to a perfusion, 1.30 mEq/l of calcium, 1.73 mEq/l of magnesium and 3.03 mEq/l of chloride were added to the artificial CSF, and then 25 to 30 mg of inulin was added to 100 ml of this artificial CSF to make up 25 to 30 mg% inulin contained solution as an inflow fluid. The schema of the perfusion system is shown in Fig. 2.

After tubing system being completed, experiments of perfusion were started. Initial 30 to 40 minute samples were discarded, since this much of time was



$$\text{OUTFLOW} = \text{INFLOW} + \text{FORMATION} - \text{ABSORPTION}$$

$$\text{FORMATION} = \text{OUTFLOW} - \text{INFLOW} + \text{ABSORPTION}$$

FIG. 2. Schema of ventriculo-cisternal perfusion system.

necessary for the displacement of fluid in the ventricular system with the artificial CSF.

The first series of experiments of ventriculo-cisternal perfusion were carried out with the pressure being changed two to four times. Sampling was started about half an hour after the intravenous dexamethasone administration of 0.15 mg per kg of body weight. At the each pressure, two ten minute samples were obtained. Between the each pressure, 20 to 30 minutes was required to get stable state of the perfusion system. Samples were taken accurately for 10 min. and cerebrospinal fluid pressure (CSFP) and superior sagittal sinus pressure (SSVP) were simultaneously recorded. CSFP and SSVP were read on the same scale with the external auditory meatus being zero point. This experiment was performed in both cases of dogs with or without dexamethasone administration.

In the second series of experiments, perfusion was put into practice without changing the height of the outlet tube. Some ten minute samples were taken exactly every 20 minutes after giving dexamethasone in the same dosis as the first series of experiments.

The chemically cleaned 15 ml flasks were weighed on an analysis balance prior to the experiment and these were weighed immediately after taking the samples on the same balance. This balance was provided with  $\pm 0.1$  mg accuracy of the optical range. Any evaporation was avoided by putting parafilm on the tops of flasks between taking samples and weighing them.

After the precipitation of proteins, determination of inulin in each sample was carried out by means of resorcinol, referred by George E. Schreiner<sup>10)</sup>. Spectrophotometry with a Shimazu Electrophotometer was performed at the wave length of 490 millimicrons on samples, inflow fluid and standard fluids. Two series of each sample were made to minimize the technical errors on diluting, pipetting and reading of the photometer.

#### *D) Cerebral Blood Flow*

Only two dogs were undergone in this experiment. These dogs were anesthetized and the respiration was controlled exactly in the same way to the perfusion experiment. In 24 hours after head injury, dogs were placed on an operating table with the inhalation of the air containing of 15% N<sub>2</sub>O being full in the Douglas bag which was connected with the respirator. Injecting 2 mg of heparin per kg of body weight intravenously, two 6 minute blood samples were taken before the intravenous administration of dexamethasone and 20 to 40 minutes thereafter. Blood from the cerebral vein was collected from a fine polyethylene catheter of 0.5 mm in inner diameter inserted into the confluence sinus through the superior cerebral vein, and arterial blood was collected from the same sized catheter introduced into the femoral artery. Analysis of gas

and calculation of CBF were made by Aizawa's modification of Kety and Schmidt's method<sup>11</sup>.

#### *E) Determination of Water Content*

Immediately after perfusion experiments, the brain was dissected out and unilateral hemisphere was separated into the gray and the white matter and water content of each structure was measured from its weight in wet and dry. Previously weighed aluminum foil planchettes were used in weighing the samples and the wet weight was recorded. The dry weight was determined after overnight desiccation at 100°C. A percentage of dry weight was determined by the formula: dry weight/wet weight  $\times 100$ <sup>12</sup>.

#### *F) Preparation to Histology*

The other half of the brain was fixed in 10% formalin solution for histological investigation with hematoxylin-eosin staining.

### RESULTS

#### *A) Criteria of Cerebral Edema*

Dogs with their heads shaken were observed comatose for several hours after shaking. Twenty four hours later, they were awake but unable to walk or feed by themselves because of vomiting. Characteristic histological findings of these dogs' brains were some degenerative changes of the glias, *i.e.* vacuolation, chromatolysis, swelling, pyknosis, and also dilatation of venules and arteries occasionally with some petechial bleeding in the gray matter. The axis-cylinders showed diffuse swelling and their courses were in disorder and twisted in the white matter. There was no any noticeable difference between two groups of the dogs with and without intravenous dexamethasone (Figs. 3 a to 3 d).

Water content of these dogs' brains was 1% higher in the white matter and 2% higher in the gray matter than that of normal dogs reported by Torii<sup>13</sup> (Table 1).

#### *B) Cerebral Blood Flow*

The mean average of shaken dogs' CBF was 15.2 ml/100 g of brain/min. This was 30% of normal dog's CBF which was 51.0 ml per 100 g of brain/min referred by Shibata<sup>14</sup>. This declined CBF of dogs with their heads shaken was slightly elevated up to 19.1 ml/100 g of brain/min about 30 minutes after the intravenous dexamethasone administration.

#### *C) Cerebrospinal Fluid Formation and Absorption Rates*

Pappenheimer *et al.*<sup>7</sup> and Heisey *et al.*<sup>8</sup> presented the reports in which methods of ventriculo-cisternal perfusion and calculation of the cerebrospinal fluid formation and absorption rates were detailed. According to them, diffusion

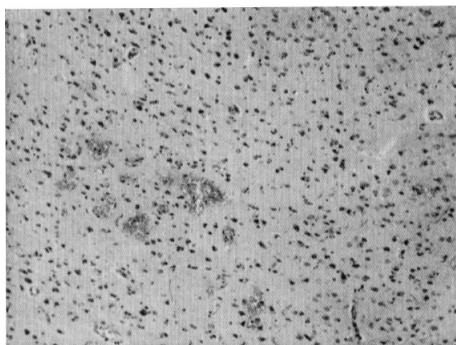


FIG. 3 a

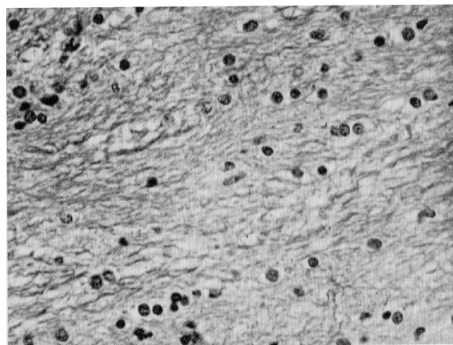


FIG. 3 b

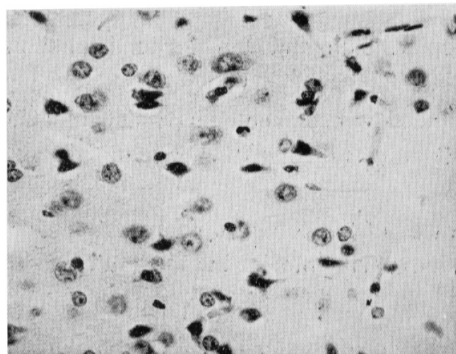


FIG. 3 c

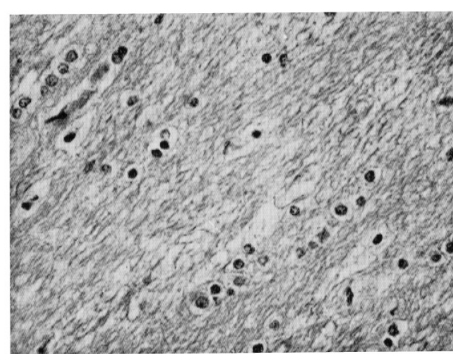


FIG. 3 d

- FIG. 3 a. The gray matter of the dog with his head shaken.  
 FIG. 3 b. The white matter of the same dog as Fig. 3 a.  
 FIG. 3 c. The gray matter of the dog with his head shaken about 3 hours after intravenously administered dexamethasone.  
 FIG. 3 d. The white matter of the same dog as Fig. 3 c.

TABLE 1. Water content of dogs' brains, calculated by the formula:

$$\text{WATER (\%)} = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100$$

	WATER CONTENT	
	GRAY MATTER %	WHITE MATTER %
NORMAL	77.14±0.76	67.99±1.38
EDEMA	80.71±1.38	69.01±1.53
EDEMA+DEXAMETHASONE	79.51±2.15	68.68±1.68

of inulin from the ventricular system was negligible, and therefore almost all inulin lost from CSF could be accounted for by bulk absorption distal to the fourth ventricle. When the outflow volume was equal to the inflow volume, the rate of absorption was equal to the rate of the cerebrospinal fluid forma-

tion. They asserted that the rate of formation was equal to outflow-inflow differences plus inulin clearance, and moreover that a linear function between the rate of absorption and CSF hydrostatic pressure existed.

Bering and Sato<sup>6)</sup> calculated the formation and absorption rates of CSF in the normal dogs. According to their document, the effective hydrostatic pressure in an animal was the difference between the pressure of the cerebrospinal fluid and the venous pressure of the superior sagittal sinus.

The formation and absorption rates of CSF in the normal dog ( $V_f$  and  $V_a$ ) were given as following formulas<sup>6)</sup>;

$$V_f = .084 (\pm .008) - .031 (\pm .032) \times 10^{-3} (\text{CSFP} - \text{SSVP}) \text{ ml/min}$$

$$V_a = .017 (\pm .006) - .438 (\pm .089) \times 10^{-3} (\text{CSFP} - \text{SSVP}) \text{ ml/min.}$$

Where CSFP and SSVP stand for cerebrospinal fluid and superior sagittal sinus pressure.

When the inflow rate was equal to the outflow rate, the effective hydrostatic pressure, *i.e.* CSFP - SSVP, was 66 mmH<sub>2</sub>O, and the formation rate of CSF was 0.046 ml per min<sup>6)</sup>.

By the first series of this study, the rates of the cerebrospinal fluid production ( $V_fE$ ) and absorption ( $V_aE$ ) in the experimentally induced edematous brain were resulted as following formulas<sup>5)</sup>;

$$V_fE = .045 (\pm .013) - .098 (\pm .079) \times 10^{-3} (\text{CSFP} - \text{SSVP}) \text{ ml/min}$$

$$V_aE = .003 (\pm .004) + .257 (\pm .379) \times 10^{-3} (\text{CSFP} - \text{SSVP}) \text{ ml/min.}$$

Cerebrospinal fluid production and absorption rates of edematous brain in the dogs who were given intravenous dexamethasone ( $V_fED$  and  $V_aED$ ) were followed;

$$V_fED = .033 (\pm .022) - .064 (\pm .107) \times 10^{-3} (\text{CSFP} - \text{SSVP}) \text{ ml/min}$$

$$V_aED = -.037 (\pm .030) + .454 (\pm .490) \times 10^{-3} (\text{CSFP} - \text{SSVP}) \text{ ml/min.}$$

When the outflow rate was equal to the inflow rate, CSFP - SSVP was 117 mmH<sub>2</sub>O and the cerebrospinal fluid production rate was 0.033 ml per min in the edematous brain. However, in dexamethasone injected edematous brain, CSFP - SSVP was 132 mmH<sub>2</sub>O and the cerebrospinal fluid production rate was 0.025 ml per min as the inflow rate was equal to outflow. These were shown graphically in Fig. 4, Fig. 5 and Fig. 6.

In the second series of this experiments, the cerebrospinal fluid production rate was observed in five dogs with their heads shaken who were intravenously administered dexamethasone, without changing the outlet height of the outflow tube during the perfusion. In these a slight increase of the cerebrospinal fluid production rate was observed at first, and the reduction of it became dominant



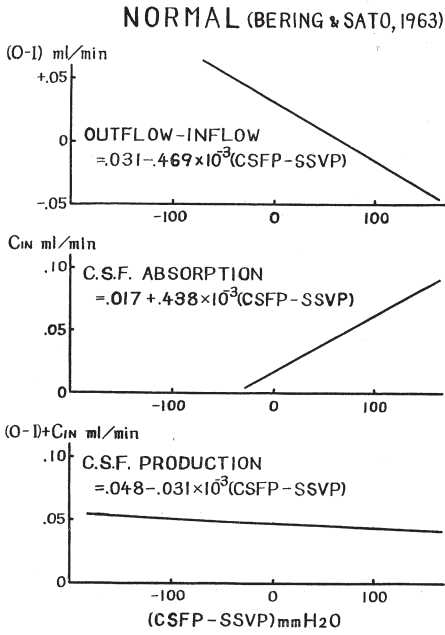


FIG. 4. C.S.F. production and absorption rates in normal dogs.

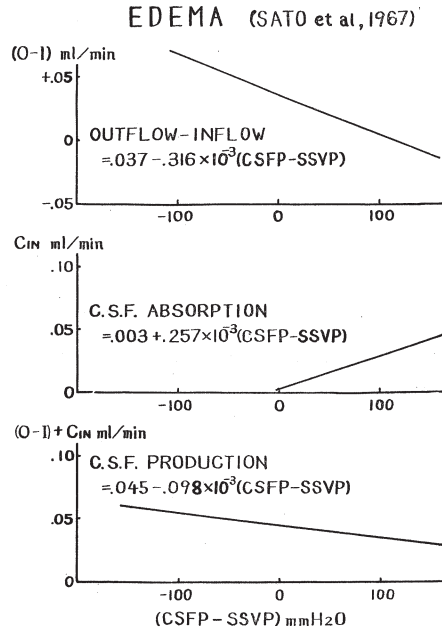


FIG. 5. C.S.F. production and absorption rates in dogs with brain edema.

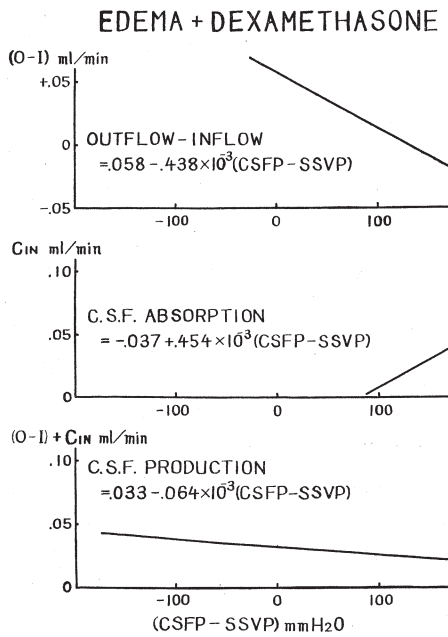


FIG. 6. C.S.F. production and absorption rates in dogs with brain edema after intravenous dexamethasone,

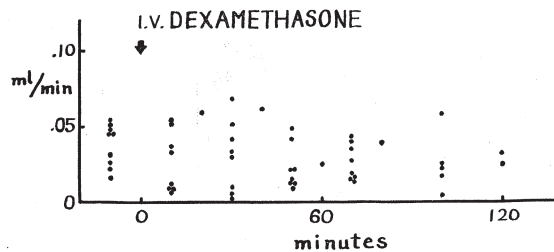


FIG. 7. Changes in C.S.F. production rate after intravenous dexamethasone.

about 60 minutes after intravenous dexamethasone and then the rate increased gradually (Fig. 7).

#### DISCUSSION

Many methods to produce the experimental cerebral edema were reported up to date. Several examples are shown as follows;

- 1) Local freezing of the surface of the brain by Clasen *et al.*<sup>15)</sup>, Klatzo *et al.*<sup>16)</sup> and Torack *et al.*<sup>17)</sup>.
- 2) Implantation of a dry psyllium seed into the brain substance by Sperl *et al.*<sup>18)</sup>
- 3) Slowly and gradually inflated balloon placed into the extradural space by Ishii *et al.*<sup>19)20)</sup> and Raimondi *et al.*<sup>21)</sup>
- 4) Brain exposure to air by Samojariski and Moody<sup>22)</sup>, Pappius and Gulti<sup>23)</sup> and Luse and Harris<sup>24)</sup>.
- 5) The intravenous administration of distilled water by Luse and Harris<sup>25)</sup> and Rosomoff and Zugibe<sup>26)</sup>.
- 6) Injection of cottonseed oil into the carotid arteries by Edstrom and Essex<sup>27)</sup> and Blinderman *et al.*<sup>28)</sup>
- 7) Triethyl tin intoxication by Magee *et al.*<sup>29)</sup>, later Aleu *et al.*<sup>30)</sup> and Torack *et al.*<sup>31)</sup>
- 8) Inoculation of tumor into the brain by Chou<sup>32)</sup> and later Aleu *et al.*<sup>33)</sup>
- 9) X-ray radiation by Clemente *et al.*<sup>34)</sup> and alpha particle radiation by Klatzo *et al.*<sup>35)</sup>

The local injury methods described above were not suitable to present studies, since perfusion experiments were in need of a diffuse cerebral edema of constant degree. Injection of distilled water or vegetable oil was avoided, for it was thought that those injection induced to destroy the blood vessels in the choroid plexus. The shaking machine newly designed produced almost satisfactorily the constant and diffuse brain edema for perfusions.

In spite of critical studies by many investigators, there is too little data to identify a common denominator of altered structure among these various studies.

It seems that today's concept of cerebral edema is said to be intracellular swellings in the gray matter and increased extracellular space in the white matter. In the injured brain, blood-brain barrier might be broken down, water-transport system of the cell membrane might be strained and fluid accumulation should occur in the central nervous system.

The first reasonable reduction of intracranial pressure was made by Weed and McKibben<sup>36,37)</sup> in 1919 who injected various hypertonic salt solutions intravenously to decrease the cerebrospinal fluid pressure. Thereafter, several hypertonic solutions have been employed to reduce the increased intracranial pressure, *i.e.* urea by Fremont-Smith and Forbes<sup>38)</sup> in 1927, sucrose by Bullock *et al.*<sup>39)</sup> and Gregersen and Wright<sup>40)</sup> in 1935, sorbitol by Schwartz and Elman<sup>41)</sup> in 1938, Wise and Chater<sup>42,43)</sup> in 1961, Shenkin *et al.*<sup>44)</sup> in 1962 and Wise<sup>45)</sup> in 1963, glycerol by Cantore *et al.*<sup>46)</sup> in 1964.

It is an agreeable thought that these hypertonic solutions might not act to repair directly the broken down blood-brain barrier, but carry out increased water in the tissues into the circulatory system by means of their osmotic action.

On the other hand, the mechanism of corticosteroid to prevent the development of cerebral edema and to reduce it has not been clarified as yet, but it may be thought that corticosteroids probably pass across the blood-brain barrier and directly act to various cells. The influences of steroid hormones upon cerebral edema were reported by many investigators up to date. Prados, Strowger and Feindel<sup>1)</sup> in 1945 found that experimental cerebral edema produced by exposure of the cerebral hemisphere to air could be prevented by the administration of adrenal cortical extract or of extracts of the anterior pituitary gland containing the adrenocorticotrophic factor. Grenell and McCawley<sup>47)</sup> in 1947 obtained the evidence that adrenal cortical extract passed across the blood-brain barrier, and showed that adequate doses of adrenal cortical extracts protected the cerebral cortex against structural and functional alteration elicited by exposure to air. Lippert *et al.*<sup>48)</sup> in 1960 studied the effect of cortisone on cerebral edema produced experimentally by subcortical implantation of psyllium seeds. They showed in the dog experiment the improvement in morbidity, mortality and severity of edema. Blinderman *et al.*<sup>28)</sup> in 1962 said that corticosteroids seemed to exert its effect by moving solutes in solution, and to strengthen the cell and its membrane by its anti-inflammatory and "anti-upsetting" role.

There is, as yet, too little reports about influences of corticosteroids upon the cerebrospinal fluid production and absorption system. In 1965, Garcia-Bengochea<sup>2)</sup> observed the decrease of the cerebrospinal fluid production in cortisone injected cats. He asserted that the reduction in the volume of CSF after cortisone acetate could be due to increased total fluid loss, particularly

on account of augmented diuresis. In his experiment, collection of CSF was by spinal catheterization. In 1967 Sato claimed in his paper<sup>4)</sup> that the former's method could not provide any exact measurement of the cerebrospinal fluid production rate. Ventriculo-cisternal perfusion used inulin contained artificial CSF was performed by Sato and was resulted that 50% decrease of the cerebrospinal fluid production compared with normal dogs was observed in the dexamethasone injected dogs.

By the same method, the cerebrospinal fluid production rate of the edematous brain was down to 0.033 ml per min. It is agreeable that this reduction might be particularly due to the decrement of CBF. The slight elevation of the cerebrospinal fluid production rate about 30 minutes after intravenous dexamethasone is occurred probably as a result of the increasing CBF depended on withdrawal of water from brain bulk. Previous workers<sup>49)</sup> said that steroids were relatively slowly absorbed and were slow in action, but the rather rapid influences of intravenous dexamethasone upon the cerebrospinal fluid production rate in the edematous brain were observed in this series of experiments.

Average production rate of CSF after dexamethasone is decreased compared with that of edematous dogs without dexamethasone. This suggests that the action of dexamethasone should be in close connection with water-ion transport of the cerebrospinal fluid secretion system.

#### SUMMARY

1) The cerebrospinal fluid production rate in edematous dogs with and without intravenous dexamethasone was studied by means of a controlled ventriculo-cisternal perfusion with inulin containing buffer.

2) A newly designed shaking machine was used in order to produce the experimental cerebral edema in dogs. In these dogs' brains, evidence was obtained of edematous changes in the histological study and water content was 1% increased in the white matter and 2% in the gray matter.

3) CBF of edematous brains in these dogs was decreased to 30% of the normal.

4) The cerebrospinal fluid production rate in the edematous brain was 0.033 ml/min, about 70% of the normal.

5) The cerebrospinal fluid production rate in the edematous brain after the intravenous injection of dexamethasone was 0.025 ml/min, about 50% of the normal.

6) Rather rapid influence of dexamethasone upon the experimentally induced edematous brain was observed; that is the initial increase which was followed by the decrease of the cerebrospinal fluid production rate after intravenous dexamethasone.

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