Cerebral Hypothermia by Ventricular Perfusion

Shunji TOKUOKA, Hideo AOKI,
Kenichiro HIGASHI,
Kinichiro TATEBAYASHI,
Terumi NAKAMURA, and
Ikuzo YOKOYAMA*
2nd Division, Department of Surgery Yamaguchi University, School of Medicine, Ube
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INTRODUCTION

Since LABORIT and HUGUENARD[24] established the method of hibernation anesthesia in 1951, hypothermia has not only been widely investigated experimentally but also utilized in the clinical medicine, especially in the field of cardiac and neurological surgery.[5][28][29][47]

In 1954, SAKAKIBARA,[46] KIMOTO[21] and PERKINS[41] initiated the procedure of the selective brain cooling through the outside of the skull or via the cerebral vessels, for the purpose of an application for cardiac surgery. By this procedure, the heart surgery has become enabled to be carried out safely under direct vision during a period of the artificial transient cardiac arrest.

More localized cooling in the brain was attempted by MARK and his collaborators[32] in 1961, using a slender refrigeration probe for the purpose of the production of reversible discrete lesions within the central nervous system, aiming at an application for the stereotactic surgery.

Recently, the perfusion of the cerebral ventricular system has so far been performed mainly as an approach to investigating the cerebrospinal fluid dynamics by some neurophysiologists.[40][42] Except for those maneuvers, there has been few reports concerning such procedure for any purpose.

In 1952, the ventricular perfusion from the lateral ventricle to the major cistern with warm physiological saline solution and some autonomotropic drugs was attempted by UEDA and his coworkers[51] on 23 patients with schizophrenia, expecting certain therapeutic effects.

TAKEUCHI and MORITA[49] reported some beneficial effects of the cooling perfusion of the ventricular system on some animals and a patient with hyperthermia due to tuberculous meningitis.

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* Present adress : First Ssrgical Department, Kumamoto Univirsity, School of Medicine, Kumamoto

In our laboratory, since 1955, the cooling perfusion from the lateral ventricle to the major cistern with cold Ringer's solution has been performed systematically on adult dogs. Some interesting facts such as the effect on the responsiveness of the animals were confirmed in the result of hypothermia to the localized nervous tissue near the ventricular wall.

METHODS

Adult mongrel dogs weighing from 4 to 12.5 Kg. were anesthetized by intravenous administration of approximately 30 mg. per Kg. body weight thiopental sodium, except for the animals which were tested to eliminate the effect of barbiturate.

The lateral ventricle of either side was operatively cannulated through a burr hole with a rubber tube. Another rubber tube was also inserted into the cisterna magna. In advance to the cannulation of the lateral ventricle, the dura mater was electrically coagulated so as to adhere with the arachnoid, pia and the surface of the cerebral cortex around the ridge of the burr hole. By this adhesion, perfusate should not escape into the subarachnoid space over the convexity. The entire perfusion system in completion is illustrated in Fig. 1. Cold Ringer's solution was perfused from the inflow tube in the lateral ventricle, via the third ventricle, aqueduct of Sylvius, and the fourth ventricle to the major cistern.

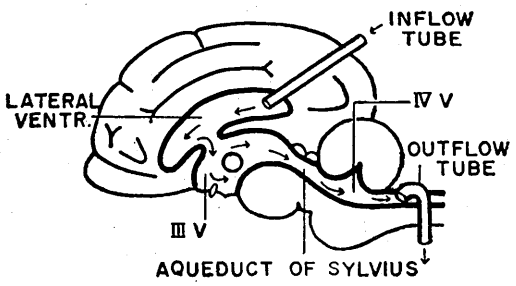


Fig. 1. An illustration of the pertusion mechanism. The inflow tube is inserted into the lateral ventricle and the outflow tube is put in the major cistern. The route of the perfusate is indicated as arrows.

An irrigator filled up with cold Ringer's solution was hung up until a suitable hight and the inflow tube was connected to the irrigator. If the tips of both tubes were properly placed in the ventricular system, there was no resistance in passage of the fluid with an adequate rate of perfusion. The rate of perfusion was easily controllable by the hight of the irrigator as well as a stop-cock inserted between the irrigator and the inflow tube.

Perfused area was tested by means of the perfusion with the fluid containing dye, and strictly limitted staining over the ventricular and aqueductal walls and the basal cisterns was confirmed. No staining of the subarachnoid space over the cerebral cortex was noted.

The operative procedure and the method of perfusion have been described in

detail elswhere in the preceding report.[14]

As soon as the condition of the animal became adequate ; half awaking state from anesthesia, in which the dog responded promptly as barking and struggling against pinching his nose but quietly laid upon unless he was stimulated, pre-experimental data were recorded and the perfusion was set out.

Temperature of the influent and effluent, state of consciousness, respiration rate, and blood pressure were monitored every 30 to 60 seconds throughout the course of experiment. The state of consciousness was mainly judged by pinching of the nose-wing with a surgical clamp. In addition, blinking reflex (reflex of orbicularis oculi), corneal reflex, and size of the pupils were also examined. Blood pressure in the femoral artery was measured directly by a U-formed column of mercury.

For the measurement of cerebral temperature, the micropyrometer with five copper-constantan thermocouples was used. Two of the thermocouples were inserted into the thalamus and the hypothalamus through a burr hole in the parietal skull of the opposite side of the cannulation, while the other two were kept towards rostral direction from the cerebellar vermis, and the rest one was placed in the major cistern for the measurement of the temperature of the effluent.

The whole brain was removed immediately after the completion of the experiment and was fixed for about a month in 10 % formaline solution. Then the sites of the tips of thermocouples were confirmed macro- and microscopically upon each frontal section of the fixed brain.

For the electroencephalographical studies, leading electrodes for surface EEG consisted of four steel needles inserted through the skull to the surface of the dura at both frontal and occipital regions. Deep EEG was obtained by the parallel steel needle electrodes inserted into the thalamus through a burr hole on the opposite side of the perfusion, leading by a micromanipulator. EEG was recorded by 8 channel inkwriting oscillograph (Toshiba). Electric stimuli (5-10 V. 10 c/sec. 0.2-0.3 msec.) were given use of a needle of the deep electrode inserted into the thalamus. After the experiment, the brain was removed and the location of the tip of the electrode was determined as same as that of thermocouples as mentioned above.

In some experiments, 6 - 9 mg. of tubocurarine chloride was injected for the purpose of preventing the interference with EMG, and respiratory arrest thereby occured was controlled by artificial breathing with oxygen.

Electron microscopical study was performed in order to elucidate the pathological changes in the brain tissue due to the cooling perfusion. One per cent osmium tetraoxide in acetate-veronal buffer solution with 0.15 M saccharose was used as fixatives. After the perfusion, brain tissues were excised as soon

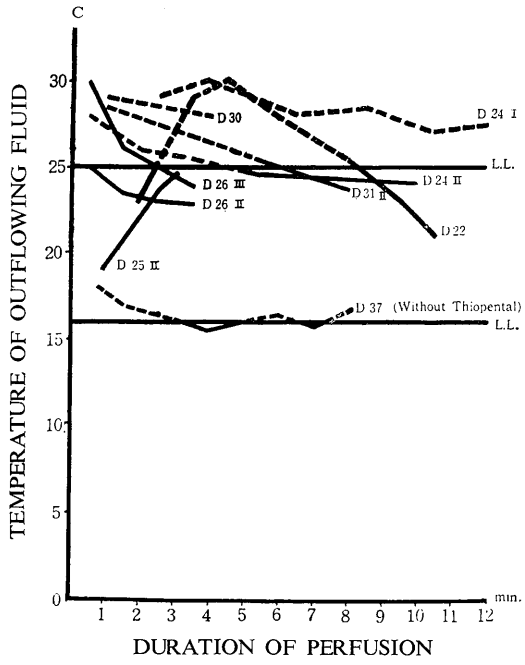
as possible. Five ml. of the fixatives were infused while the animal was alive so as to prevent autolysis of the tissues. The method of fixation and preparing the ultra-thin section has been described in detail elswhere in the previous report.[36]

CONDITION OF THE PERFUSION

Temperature of Perfusate : As shown in Table 1, the temperature of the influent measured at the point of connection between irrigator and the inflow tube was varied in the range of 7°C. to 15°C., in average 10°C., while that of the effluent was 15°C. to 28°C., in average 22°C. Measuring of the temperature of the influent was carried out immediately before and after the perfusion, while that of the effluent was measured every minutes during the perfusion.

Table 1. Condition of the Perfusion

	Range	Suitable Conditions
Temperature of Influent	7~15°C.	8°C.
Temperature of Effluent	15~28°C.	22°C.
Rate of Perfusion	20~30 ml./min.	30 ml./min.
Duration of Perfusion	3~22 min.	8 min.



Regarding the temperature of the effluent it was confirmed that there was a certain threshold in the temperature of this fluid in relation to the appearance of unresponsiveness. As shown in Fig. 2, this threshold was appeared to be 25°C., though the consumate unresponsiveness was not obtainable beyond this threshold in some cases. In the cases without thiopental sodium, the threshold was lower than the anesthetized cases ; i. e. 16°C.

Fig. 2. Interrelation between unresponsiveness obtained and temperature of the perfusate. The broken lines indicate the unextinguishable or weakened nose pinching response. The soild lines represent the abolished responses.

Rate of Perfusion: The rate of 30 ml. per minute was enough to produce the unresponsive state provided that the temperature of the perfusate was sufficiently low. Although reasonably high intracranial pressure was to be expected during the perfusion at this rate of the flow, mechanical effects against the internal wall of the ventricles would be negligible on the basis of the observation in the control experiments with warm Ringer's solution.

Duration of Perfusion: Duration of the perfusion was 8 minutes in average, varying from 3 to 22 minutes. Inspite of such a short duration, it was enough to be capable of observing the changes in general conditions, particularly the state of consciousness, because of the extreme rapidity of the appearance and disappearance of unresponsiveness, while this short unresponsive state may not be called as "anesthesia".

From our experiments, it may be conceivable that a too long duration of perfusion would result in cerebral edema, elevation of intraocular pressure and tendency to exophthalmus on the perfused side. It was proved that the restoration of the cerebral temperature required five to ten minutes following the cessation of the perfusion. Therefore, the interval of 15 to 20 minutes should be allowed for the successive perfusion on the same animal.

PHYSIOLOGICAL CHANGES DURING THE PERFUSION

Responsiveness upon the Stimulation from Outside: The responsiveness of the experimental animals was examined by the nose pinching test and the tests of blinking and corneal reflexes. Our "nose pinching test" is a test of the escape reflex of which procedure is as follows: The wing of nose, the most sensitive part in the face of dog, is pinched by the tip of a hemostatic clamp. Following this stimulus the dog in awaking state cries out, twiches his facial muscles and struggles with his limbs and tail. Slight degree of anesthesia does not interfere the responsiveness for this stimulus. Since this test is a handy method for the judgement of the consciousness of animals, the effect of the cooling perfusion on the consciousness was mainly examined by this test. The nose pinching response disappeared very rapidly in almost all cases where the cooling perfusion was performed under adequate conditions.

Under suitable conditions of the perfusion as described in Table 1, dogs became unresponsive to the external stimuli within a minute after the beginning of the perfusion.

As shown in Table 2, nose pinching response was disappeared or weakened in all of 29 cooling perfusions performed in 15 animals. In those cases which became unresponsive, the nose pinching response disappeared as rapidly as 40 seconds in average following the start of the perfusion. The recovery from the

unresponsive state was also remarkably rapid; dogs regained responsiveness to the nose pinching stimuli 33.4 seconds in average after the cessation of the perfusion. Five dogs in this series responded to the stimuli within 10 seconds after the perfusion.

Blinking reflex being provocated by touching the eye-lid and the corneal reflex are less affected than the nose pinching response. Ten per cent of these animals

Table 2. The Rate of Appearance in Physiological Changes During the Cooling Perfusion and the Control Experiments (%)

Perfusate		Cold Ringer	Warm Ringer	Hot Ringer	Cold Saline	Warm Saline
No. of Experimnet		29	8	5	8	7
Nose Pinching Response	disappeared	86.2	0	0	87.5	42.9
	weakened	13.8	0	0	0	14.2
	unchanged	0	100	100	12.5	42.9
Blinking Reflex	disappeared	55.2	0	0	62.5	0
	weakened	34.5	0	20	25.0	0
	unchanged	10.3	100	80	12.5	100
Corneal Reflex	disappeared	77.8	—	0	—	—
	weakened	0	—	0	—	—
	unchanged	22.2	—	100	—	—
Light Reflex of Pupils	disappeared	3.8	0	0	12.5	42.9
	weakened	38.5	25	20	0	14.2
	unchanged	57.7	75	80	87.5	42.9
Respiration Rates	increased	13.8	0	40	37.5	57.1
	decreased	69.0	12.5	20	50.0	28.7
	unchanged	17 2	87.5	40	12.5	14.2
Pulse Rates	increased	13.8	0	20	50.0	57.1
	decreased	62.1	12.5	60	33.3	14.2
	unchanged	24.1	87.5	20	16.7	28.7
Blood Pressure	elevated	0	0	33.3	—	—
	lowered	90.0	0	0	—	—
	unchanged	10.0	100	66.7	—	—
Size of Pupils	enlarged	7.7	12.5	40	71.4	85.7
	constricted	57.7	12.5	0	0	0
	unchanged	34.6	75.0	60	28.6	14.3
Muscle Tone	relaxed	82.8	12.5	0	37.5	42.8
	stiffened	0	0	0	37.5	28.6
	unchanged	17.2	87.5	100	25.0	28.6

well responded to the stimuli on either side of the eye-lid throughout the cooling perfusion, while in 22 per cent of them the corneal reflex was remained unchnged. However, in more than half of the cases, these reflexes were disappeared ; 55 % in the blinking reflex, and 78 % in the corneal reflex. The lapsed time before disappearance of these reflexes was longer than that of the nose pinching response, 100 seconds in average in the blinking reflex and 140 seconds in average in the corneal reflex. (Table 2)

Changes in the Pupils : In more than half of the animals size of the pupils reduced, and in only two out of 26 cases they were rendered mydriatic. As to the pathological significance of such changes in the size of pupils full information is still lacking, while in the control experiments perfused with warm Ringer's solution only few changes were observed in the size of the pupils. (Table 2)

The light reflex of the pupils was the least affected one among the reflexes tested. This reflex disappeared in only less than 4 per cent of the cases, and in more than half of them, it remained unchanged throughout the cooling perfusion. (Table 2)

Respiration : Changes in the respiration were so remarkable during the cooling perfusion that the reduction of the respiration rate was recognized in 69 per cent, probably due to the direct effect of cooling upon the respiratory center in the medulla oblongata, while it increased in 14 per cent of the cases. Here we provide to reffer the judgement of the respiration rate as follows ; increase of the rate more than 10 per minute as compared with the pre-perfusion data is described as "increased", decrease more than 10 per minute as "decreased", and changed within the range of 9 per minute as "unchanged". (Table 2)

Typical courses of the changes in respiration in six cases and the data of the controls were demonstrated in Fig. 3. Some of the illustrated cases showed initial increase of the respiration rate which was followed by gradual reduction. Following the cessation of the perfusion, with a temporary increase within two to three minutes, the respiration recovered to the normal level very rapidly. If the effects of cooling were excessive respiratory arrest occured, while this apnea could be restored and animals resumed normal deep respiration when the perfusion was ceased immediately after the developement of apnea. These respiratory arrests were encountered in 6 cases in this series.

Pulse Rate : Pulse rate decreased (more than 20 per minute from the pre-perfusion data) in 62 per cent during the cooling perfusion, while in 14 per cent it increased (nore than 20 per minute from the pre-perfusion data). In 24 per cent it remained unchanged (shifted within 19 per minute). The grade of reduction of the pulse rate was more slight than that of the respiration rate, and recovery time of the pulse rate after the cessation of the perfusion was

longer than that of the respiration rate. (Table 2 and Fig. 4)

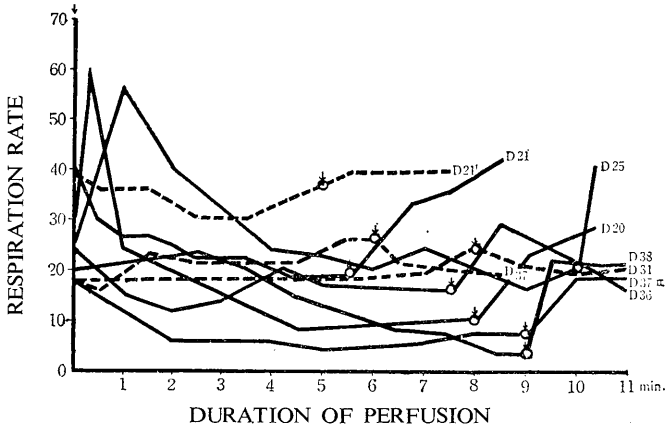


Fig. 3. Changes in the respiration rates during and after the perfusion. Solid lines indicate the cases of the cooling perfusion. Broken lines indicate the control experments with warm Ringer's solution. Cricles with arrows represent the cessation of the perfusion.

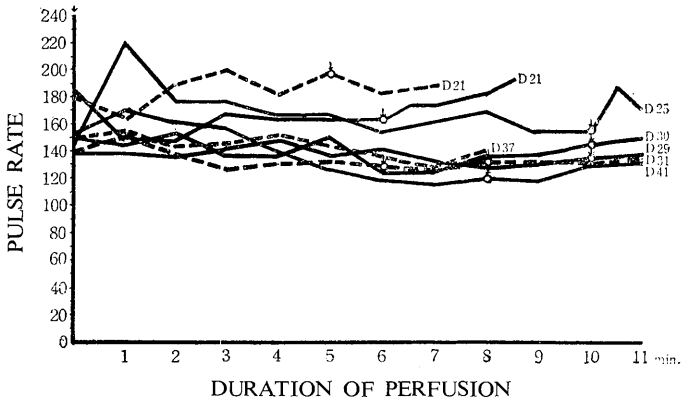


Fig. 4. Changes in the puls rates during and after the perfusion. Soild lines indicate the cases of the cooling perfusion. Broken lines indicate the control experiments with warm Ringer's solution. Circles with arrows represent the cessation of the perfusion.

Arrythmia was occationaly observed in such cases as with the respiratory arrest, while they disappeared spontaneously as soon as the respiration had recovered.

Blood Pressure : Blood Pressure was measured in ten cases. In nine of these cases (90%), fall of the blood pressure in the range of more than 20 mmHg from the levels before the perfusion, while in only one it remained

unchanged (fell less than 20 mmHg). Typical courses of the blood pressure during the cooling perfusion and those of the controls are demonstrated in Fig. 5.

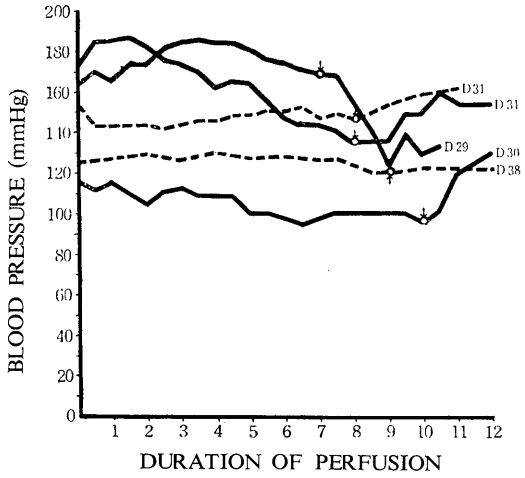


Fig. 5. Changes in the blood pressure during and after the perfusion. Solid lines indicate the cases of the cooling perfusion Broken lines indicate the control experiments with warm Ringer's solution. Circles and arrows represent the cessation of the perfusion.

Body Temperature: Rectal temperature remained unchanged throughout, while in some cases a fall whithin one half degree C. or an initial elevation within one degree C. was observed.

Muscle Tone: Majority of the cases (83%) showed the relaxation of muscles during the cooling perfusion accompanied by the unresponsiveness. None of the cases showed the stiffness of muscles.

CONTROL EXPERIMENTS

Perfusion with Warm Ringer's Solution: Under the same conditions as mentioned above, the perfusion was performed with Ringer's solution being warmed at 36°C. to 39°C. on eight dogs, and the unresponsiveness to external stimuli was not resulted in all cases. Other data related to the physiological conditions seldomly changed as shown in Table 2 and Figs. 3, 4 & 5.

Perfusion with Hot Ringer's Solution: The perfusion with Ringer's solution being warmed at 43°C. to 47°C. was performed on four dogs in five times. Diminution of the facial reflexes was scarcely observed as shown in Table 2. In all of them muscle tone was utterly unchanged, while slight acceleration of the respiration was observed in two cases. Respiratory arrest was occured in a case in which the temperature of effluent reached at 41°C., being maximal grade

in this series. Changes in the pulse rate were irregular, while significant changes in the blood pressure were not observed.

Perfusion with Cold Physiological Saline Solution : Eight cooling perfusions with physioiogical saline were performed with the different results from those with cold Ringer's solution. Nose pinching response was abolished almost always and the blinking reflex changed at similar degree in comparison with the cooling perfusion with Ringer, while acceleration of the respiration and the pulse rate was more often observed than the cold Ringer perfusion. Mydriasis was highly encountered in contrast to the cold Ringer perfusion. Tendency to rigidity was observed as the same rate with relaxation of muscles. Delay of recovery from the induced unresponsiveness and considerably severe incidents such as gross shivering, oculomotor palsy, nystagmus, hypersalivation, and convulsion were also observed during or after the perfusion (Table 2 & 3).

Perfusion with Warm Physiological Saline Solution : Seven control perfusions with physiological saline being warmed at 34°C. to 38°C. were carried out on seven dogs. In three cases of this series the nose pinching response was abolished, and weakened in a case. Tendency to mydriasis and the increase of respiration and pulse rate were observed in most of the cases, while muscle tone tended to relaxation or stiffness in 3 and 2 cases respectively. Considerable incidents were encountered in almost all cases though in the slightest degree (Table 2 & 3).

INCIDENTS AND SURVIVAL TEST

Of the series of the cooling perfusion with Ringer's solution, none showed severe incidents except for apnea, which was encountered only in such cases that were perfused too vigorously. As shown in Table 3, mild incidents such

Table 3. The Rate of Occurence in Incidents During and After the Cooling Ventericular Perfusion and the Control Experiments (%)

Perfusate	Cold Ringer	Warm Ringer	Hot Ringer	Cold Saline	Warm Saline
No. of Experiments	29	8	5	8	7
Nystagmus	17.2	0	0	12.5	14.3
Oculomotor Palsy	0	0	0	12.5	14.3
Conjugate Deviation	0	0	0	0	14.3
Exophthalmus	0	0	0	0	14.3
Hypersalivation	6.9	0	0	0	28.6
Respiratory Arrest	20.7	0	20	0	0
Arrhythmia	10.3	0	20	0	0
Shivering	0	0	0	25	0
Convulsion	0	0	0	25	0

as nystagmus, arrythmia and hypersalivation occured in a few cases, while all of them disappeared as soon as the perfusion was stopped. Rather severe incidents were more often observed in the series with saline solution as mentioned above.

All dogs being perfused with cold Ringer's solution survived except for the cases sacrificed in order to obtain the specimen of the brain after the experiment.

Survived dogs showed no ataxia excepting the cases which were stabbed the cerebellar vermis for the measurement of the brain temperature. Any significant abnormalities or disturbances in function which might be considered to be due to the cooling perfusion was not observed. Concerning the change of charactor, though details of which were impossible to be estimated, it was observed that the violent dogs tended to become more docile for a long time after the cooling perfusion.

BRAIN TEMPERATURE

Measurement of the temperature was made by means of a puncture with a thermocouple from the surface of the cerebellar vermis towards rostroventral direction, followed by progressive insertion with a rate of one to two mm. per 15 sec. using a micromanipulator during the cooling perfusion. As the result of this procedure, as shown in Fig. 6, the changes of the temperature were traced as U- or V-form curves. From these curves, it was verified that as the tip of the thermocouple approached to the cerebrospinal fluid space the regional temperature rapidly fell.

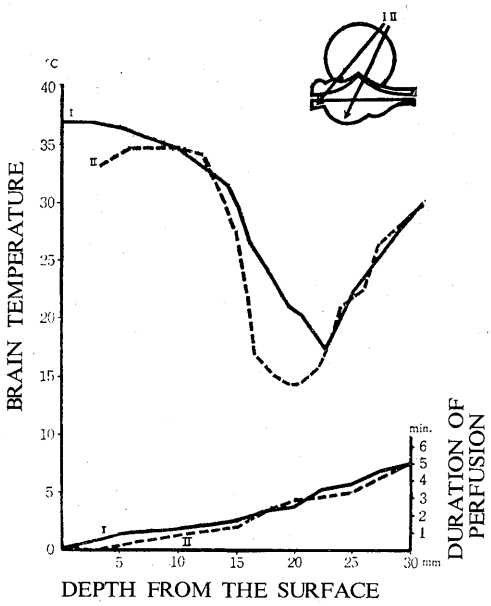


Fig. 6. Upper two curves demonstrate the local temperature at the points of various depth in the brain stem during the cooling perfusion. (D 30). Measurements performed by the direct insertion of a thermocouple from the cerebellar vermis to rostroventral direction with a rate of 1mm. per 15 sec. Curves show a V or U form, and their bottoms correspond to the period when the tip of a thermocouple was passing through the cerebrospinal fluid space.

Lower two curves demonstrate the depth of the tip of a thermocouple in the brain stem at each period of time, as is noted diagramatically at the right top corner.

Another procedure for measuring the brain temperature during the cooling perfusion was performed by placing four thermocouples in the various part of the brain; i.e., subcortical tissue, internal part of the thalamus, hypothalamus and the periaqueductal tissue. As shown in Fig. 7, in the areas being close to the ventricular wall such as the hypothalamus and the periaqueductal tissue the temperature fell rapidly from the initial stage of the perfusion, while it remained almost constant after the equilibrium was reached. After the cessation of the perfusion, the temperature rose gradually to the pre-perfusion normal level. On the other hand, in the areas being remote from the ventricular wall such as the subcortical and intrathalamic tissue, the temperature remained unchanged throughout the perfusion.

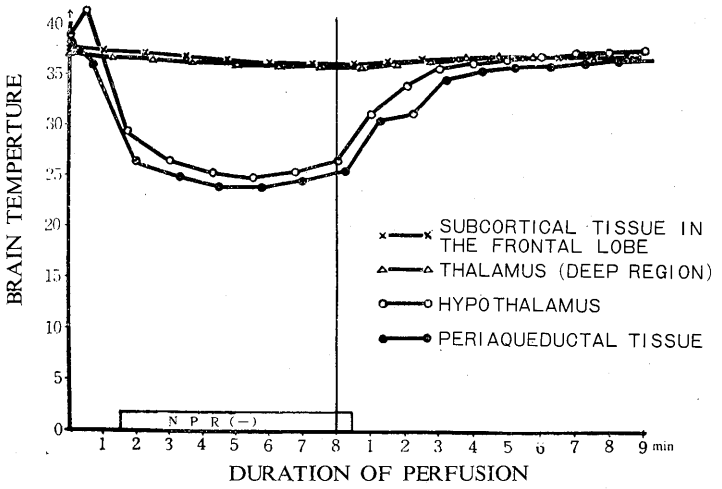


Fig. 7. Changes of the brain temperature in various regions of the brain. (D 101 ; perfused from the lateral ventricle to the major cistern with 8°C Ringer's solution at 30 ml./min. NPR was abolished from 90 sec. after the beginning of the perfusion and reappeared from 30 sec. after the cessation of it.). Figure shows steep fall of the temperature in the hypothalamus and the periaqueductal tissue and relatively plane curve in the subcortical tissue and deep part of the thalamus.

On twenty dogs the local temperature was measured in the various regions of the brain by the same method as mentioned above. Then the fall of temperature from the pre-perfusion level at the time when one minute was lapsed following the abolishment of the nose pinching response was plotted upon several transverse sections as shown in Figs. 8 and 9. Consequently, it was verified that the reduction rates of the temperature in the cerebellar vermis, periaqueductal grey matter, hypothalamus and the areas being close to the ventricular wall were larger than the others.

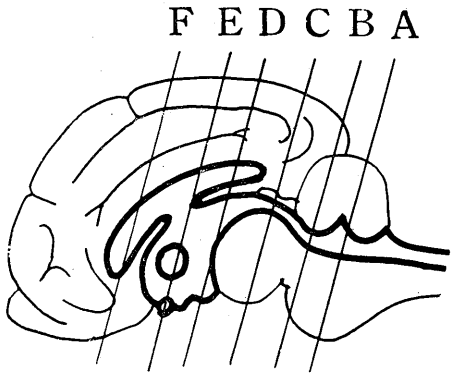


Fig. 8. Lines indicate following transverse sections. Each level corresponds to each diagram in Fig. 9.

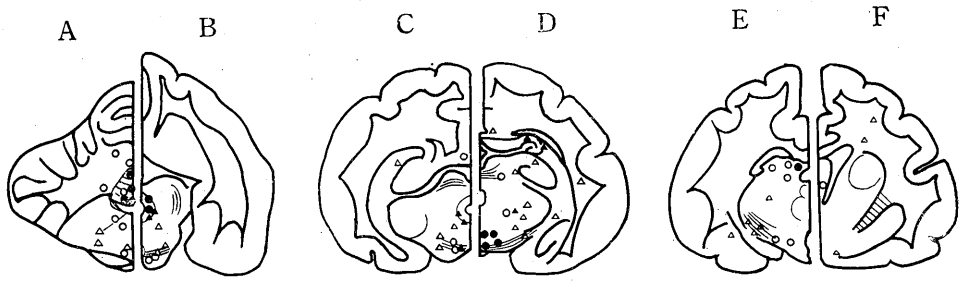


Fig. 9. Diagrams of the transverse sections of the dog's brain. Symbols on each diagram indicate the tips of thermocouples. Indication as follows: Open triangles; Fall of temperature ranging 0-4°C during the cooling perfusion. Open circles; that of 4.1-8°C. Solid triangles; that of 8.1-12°C Solid circles; that of more than 12°C.

LOCALIZED COOLING PERFUSIONS OF THE VENTRICULAR SYSTEM

Cooling Perfusion between Both Lateral Ventricles : On five dogs cold Ringer's solution was let flow from the lateral ventricle on one side to the other one. None of them became unresponsive during the cooling perfusion of this route. In addition, no significant changes were observed in the respiration, pulse rate, blood pressure, and muscle tone throughout the perfusion (Fig. 10-A).

Cooling Perfusion from the Third Ventricle to the Major Cistern : the inflow tube was operatively inserted into the third ventricle through the rostral part in three dogs and through the caudal part in one. During the cooling perfusion, satisfactory unresponsive state was obtained in all of these four cases. After the perfusion, it was verified by perfusion of dye that the lateral ventricles were not involved in the flow of the perfusate. (Fig. 10-B & C).

Cooling Perfusion of the Fourth Ventricle by Means of the Insertion of a Double Tube from the Major Cistern : In this procedure the influent flows through the thin tube into the fourth ventricle and the effluent flows out through

the thick tube surrounded the inflow tube as indicated in the Fig. 10-D & E. Eight dogs were perfused by this procedure. Five of them in which the perfused area was limitted within only the fourth ventricle and the caudal end of the aqueduct of Sylvius (Fig. 10-D), were not rendered to be unresponsive with an exception in which the nose pinching response was merely weakened. On the other hand, three of them, which were perfused so extensively that the aqueduct and the entire ventricle were involved due to the excessive high pressure of the perfusion or to the excessively deep insertion of the inflow tube (Fig. 10-E), were rendered unresponsive completely. The perfused area was also verified with dye.

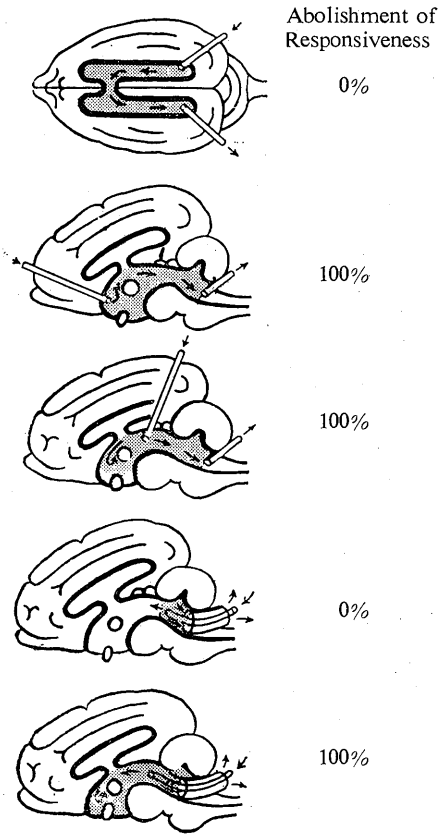


Fig. 10. Illustrations of the several procedures for localized cooling ventricular perfusion. Arrows indicate the direction of flow. The effects of these localized cooling perfusion on the responsiveness are noted on the right.

ELECTROENCEPHALOGRAPHIC STUDIES

Forty-three ventricular perfusions were performed on 26 dogs for the purpose of the study with electroencephalography. Cold Ringer's solution (5°C) was

used in 39 of them as the perfusate, hot (39°C) and warm (37°C) solutions were employed in remaining each two animals. Seventeen cooling perfusions were carried out under the condition of spontaneous breathing, while in 22 artificial respiration was applied, with pure oxygen including 20 dogs treated with tubocurarine chloride.

In 21 observations no alteration in EEG paterns was remarked during and after the cooling perfusion in spite of the development of unresponsiveness (Fig. 11). However, if the respiration was severely affected ; under such condition that the temperature of the effluent reached below 19°C and the rate of perfusion exceeded the limit of 30 ml/sec., low voltage slow waves developped on EEG leading to the loss of activity. This depressed activity recovered when the animal resumed the spontaneous respiration after the cessation of the perfusion (Fig. 12).

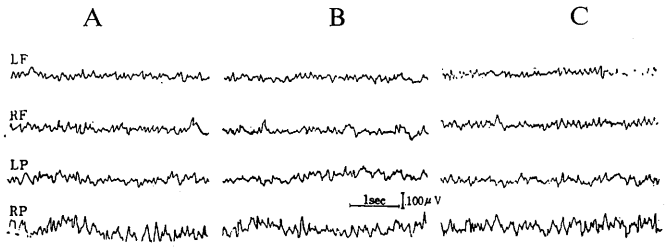


Fig. 11. Surface EEG during the cooling ventricular perfusion. Conditions of the perfusion as follows : Temperature of influent ; 5～7°C. Temperature of effluent : 20～23°C. Rate of perfusion ; 25～30 ml/sec. Duration of perfusion ; 5～10 min.
A : Before the perfusion. B : One min. after the beginning of the perfusion. C : 40 sec. after the cessation of the perfusion.

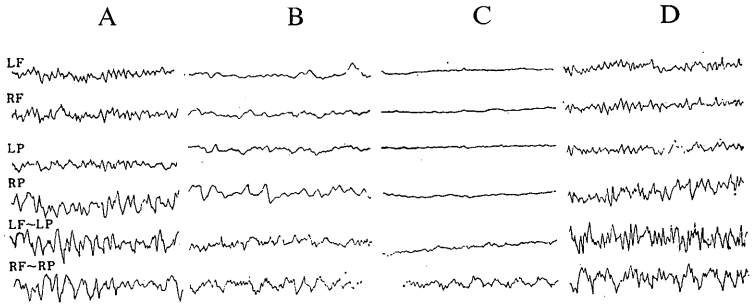


Fig. 12. Surface EEG during and after the cooling ventricular perfusion with excessive cooling. Conditions of the perfusion were as follows : Temperature of influent ; 3～5°C. Temperature of effluent ; 15～19°C. Rate of perfusion ; 32～36 ml/sec. Duration of perfusion ; 6 min.
A : Before the perfusion. B : 5 min. after the beginning of perfusion. C : 5½ min. after the beginning of perfusion. D : 2 min after the cessation of perfusion.

Most of the EEG records during the cooling perfusion were characterized by bursts of approximately 8 c/sec. lasting 1-2 seconds appeared at an initial stage of the perfusion. Naturally these bursts were regarded as the same nature with the barbiturate bursts, since the perfusion was carried out under slight barbiturate anesthesia. However, it was significant that the appearance of these bursts was more frequent in this particular stage of the cooling perfusion even though the true barbiturate bursts were scattered on the background activities of the pre-perfusion record. "Nose pinching bursts", otherwies, which were evoked by pinching the nose of dog were also appeared transiently in the initial stage of the cooling perfusion. Since these bursts were even appeared with blocking the neuromuscular junction by the injection of tubocurarine chloride, electromyogram must not be responsible for these bursts.

As shown in Fig. 13, neither the barbiturate bursts nor the nose pinching bursts appeared during the cooling perfusion, while they reappeared shortly after the cessation of the perfusion.

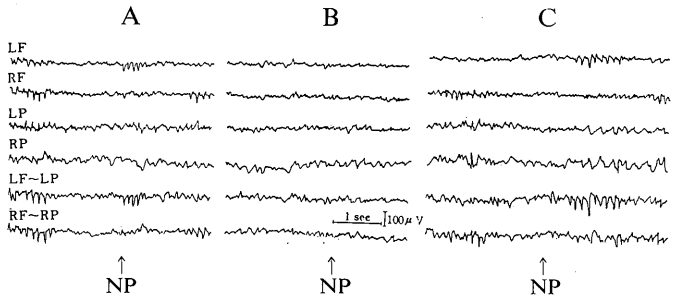


Fig. 13. Effects of the cooling ventricular perfusion on the barbiturate bursts and the "nose pinching bursts."
A: Pre-perfusing record of surface EEG. Barbiturate and nose pinching bursts are seen in all areas. B: 80 sec. after the beginning of perfusion. Bursts disappeared. C: 80 sec. after the cessation of perfusion. Bursts reappeard.
Arrows indicate the application of nose pinching.

On the ventricular perfusion with warm or hot Ringer's solution, EMG was recorded by the nose pinching stimuli (Fig. 14). However, when the ventricles were perfused with cold solution, such EMG was abolished (Fig. 15). This abolishment of EMG was also accompanied by disappearance of the nose pinching response, while the basic pattern of EEG was never changed even in this stage of unresponsiveness.

Nine recordings of deep EEG were obtained in the cerebral cortex and the thalamus under the cooling perfusion. Histological detections indicated that the site of the deep electrodes corresponded to following locations: nucleus centralis medialis, nucleus medialis dorsalis, nucleus commissurae posterioris, zona incerta proper and nucleus reticularis.

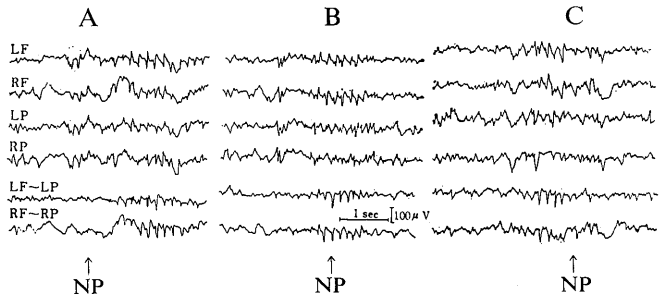


Fig. 14. "Nose pinching bursts" during and after the ventricular perfusion with warm Ringer's solution.
A: Pre-perfusion record of surface EEG. B: 2 min. after the beginning of perfusion. C: 3 min. after the cessation of perfusion.
Arrows indicate the application of nose pinching.

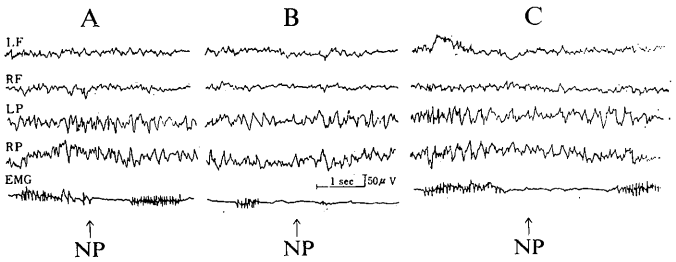


Fig. 15. Effects of the cooling ventricular perfusion on the myogram elicited by nose pinching.
A: Pre-perfusing record of EEG and EMG. B: 80 sec. after the beginning of perfusion. C: 40 sec. after the cessation of perfusion.
Arrows indicate the application of nose pinching.

In the results, deep EEG records showed identical patterns as those observed on the surface EEG not only in the subcortical tissue but also in the thalamus. Namely, when the EEG records from the scalp were normal, deep EEG was also unchanged, and the bursts or low voltage slow waves were simultaneously recorded on both of the surface and deep EEG (Figs. 16 & 17).

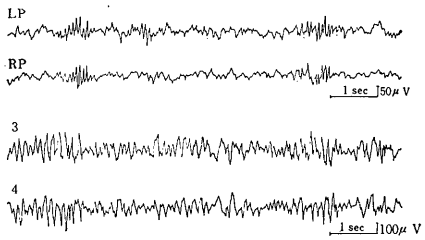


Fig. 16. Surface and deep EEG showing the spontaneous burste immediately after the beginning of the cooling ventricular perfusion.
LP, RP: Surface EEG. 3: Deep EEG recorded from nucleus commisurae posterioris. 4: Deep EEG recorded from nucleus centralis medialis.

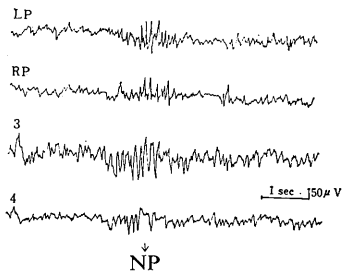


Fig. 17. Surface and deep EEG showing "nose pinching bursts" immediately after the beginning of the cooling ventricular perfusion.
LP, RP: Surface EEG. 3: Deep EEG recorded from nucleus medialis dorsalis. 4: Deep EEG recorded from nucleus caudatus.
Arrow indicates the application of nose pinching.

Two parallel needles were inserted into the thalamus from the cerebral surface of the opposite hemisphere of the cannulation, with a distance of about 10 mm. each other. Then, as repetitive electrical stimuli were given on one electrode, the synchronized activity was recorded on another one. The synchronized waves were hardly observed on the scalp EEG especially under the slight anesthesia, and they remained unchanged during the cooling perfusion in spite of disappearance of the barbiturate bursts (Fig. 18).

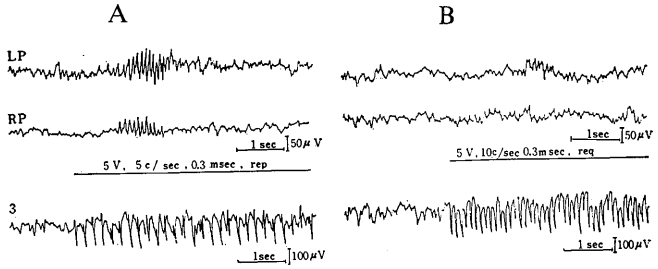


Fig. 18. Responses of the thalamic electrical stimulation on EEG.
A: Pre-perfusing record of surface and deep EEG. B: During the cooling ventricular perfusion.
LP, RP: Surface EEG. 3: Synchronized waves recorded from nucleus centralis medialis during application of the repetitive electrical stimuli to nucleus commissurae posterioris.
Bars in the middle indicate the application of the repetitive electrical stimuli.

ELECTRON MICROSCOPICAL OBSERVATIONS OF THE CEREBRAL SUBSTANCE NEAR THE VENTRICULAR CAVITY

In order to investigate the pathological changes such as brain edema in the post-perfused brain, electron microscopy was employed. On the standpoint of recent advance in the knowledge about the ultrafine structure of the brain tissues especially that of brain edema, it is considered that the electron microscopical study gives more accurate informations than the light microscopy as an approach to the pathology of the post-perfused brain.

Electron microscopical pictures of the cerebral tissue close to the ependymal lining in the lateral ventricle of normal dog were characterized by following

features. Ependymal cells in the ventricular wall had a moderately abundant and relatively clear cytoplasm. And near the nucleus, fine fibrils of 75 to 100 Å in diameter were seen characteristically. Especially, on the ventricular surface of the cytoplasm cilliary shafts were observed (Fig. 19).

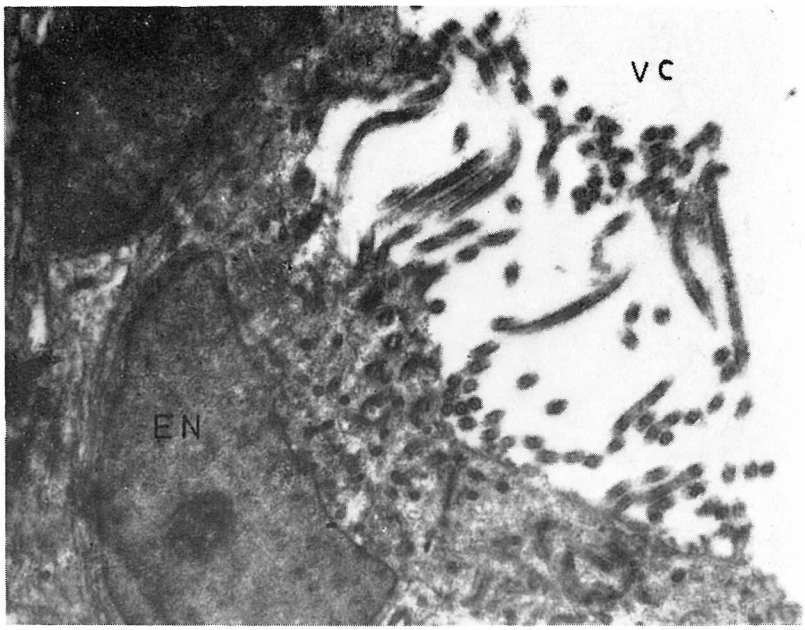


Fig. 19. Normal ependymal cell. The cell has relatively clear cytoplasm. On the surface fronting to the ventricular cavity the ciliary shafts are seen (×10000). EN: Ependyma cell nucleus. VC: Ventricular caviey.

Under the ependymal cell, many myelinated nerve fibers were seen and occasionally astrocyte, oligodendroglia and microglia were recognized. Astrocytes were usually considered to have clear "watery" cytoplasm with no granular endoplasmic reticulum, relatively few mitochondria and clear processes. However, the nerve cells and the blood capillaries were rarely found. The intercellular space was as narrow as about 100 to 200 Å. Capillaries were surrounded by the clear glial processes containing a few mitochondria and endoplasmic reticulum (Fig. 20).

Electron microscopical pictures of above tissues after the cooling ventricular perfusion are demonstrated in Figs. 21 and 22. The most outstanding changes in these pictures in comparison with those of the normal animal were enlargement of the clear glial processes and swelling of the mitochondria particularly around the pericapillary space (Fig. 21). However, comparing to the electron microscopical findings of the experimental cerebral edema which have been reported by several investigators,[19)25)30)] these changes were relatively mild in severity. Some mitochondriae in the clear processes located in the pericapillary space were swollen and occasionally gathered near the basement membrane of the capillary (Fig. 22).

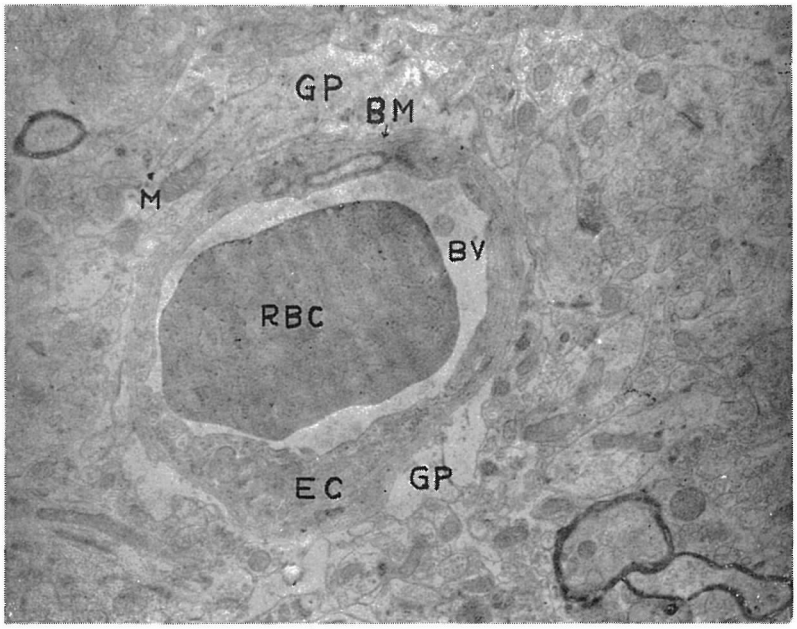


Fig. 20. Normal capillary blood vessel in the brain. The capillary is surrounded by the clear glial processes. No space is observed between the basal membrane of the blood vessel and the cytoplasm of the glial cell. (x9200)
BM : Basal membrane. BV : Blood vessel. EC : Endothelial cell. GP : Clear glial process. M : Mitochondria. RBC : Red blood cell.

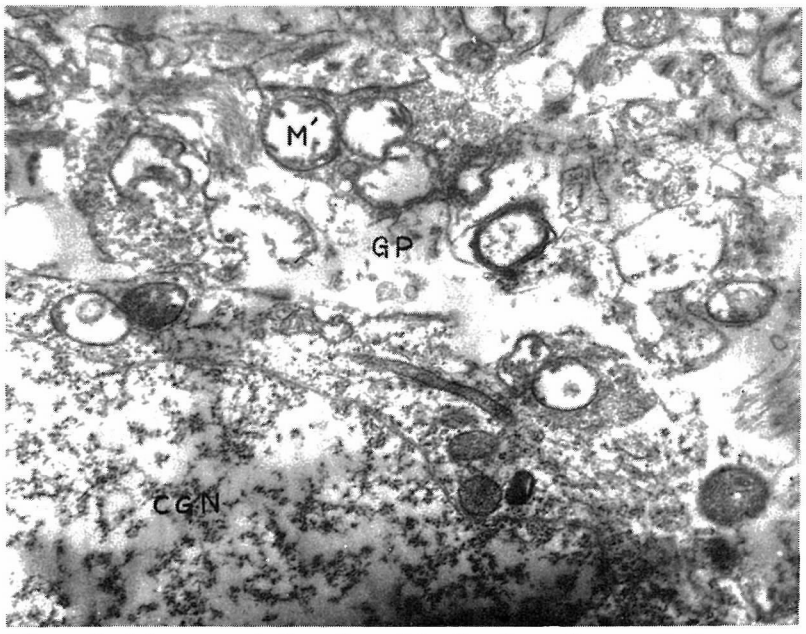


Fig. 21. The cerebral tissue near the lateral ventricle after the cooling ventricular perfusion. The clear glial process reveals decreased density. The right portion shows fine fibrils. (x12400).
CGN : Clear glial cell nucleus. GP : Clear glial process. M' : Swelling mitochondria.

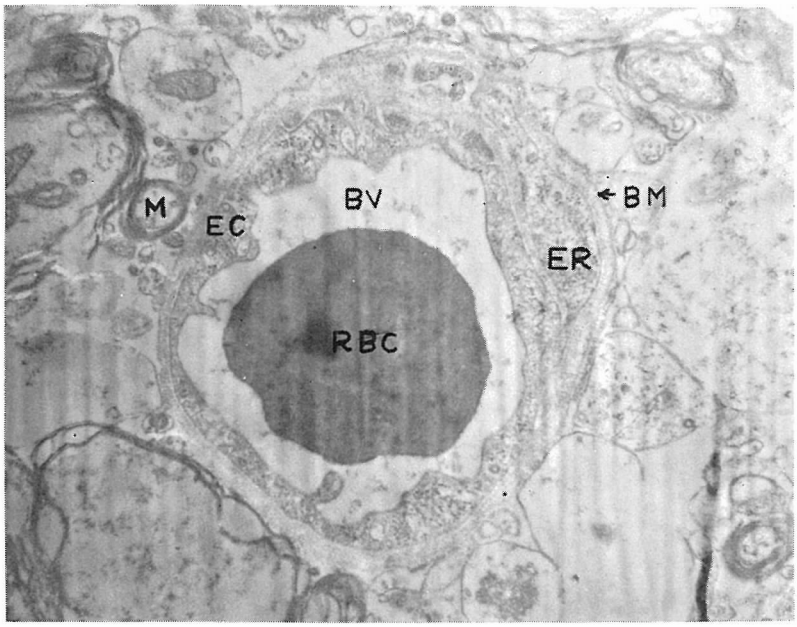


Fig. 22. Transverse section of the capillary blood vessel near the wall of the third ventricle after the cooling ventricular perfusion. Glial processes around the blood vessel shows increased volume with resultant markedly decreased density. In the endothelial cells, the endoplasmic reticulum is increased in number and its width (x12400).
BM : Basal membrane. BV : Blood vessel. EC : Endothelial cell. ER : Endoplasmic reticulum. RBC : Red blood cell. M : Mitochondria

The capillaries which were surrounded almost completely by the myelinated nerve fibers showed no significant changes. Furthermore, the glial cell, nerve cell and their processes in the other places revealed no alterations.

Summarizing above results, the cooling perfusion did not cause the dilataion of the intracellular space, but only brought about swelling of the glial processes at the vicinity of the capillaries. This alteration, however, was relatively slight. The ependymal cell showed no significant changes.

CLINICAL EXPERIENCES

Cooling perfusion of the cerebral ventricular system with cold Ringer's solution was attempted on three psychopathic patients who had frequently suffered from violent attacks, with an expectation of obtaining the same therapeutic effects as the shock-therapy or leucotomy (Table 3 & 4).

Following conditions of perfusion were found to be optimal: Temperature of the influent; about 8°C. Temperature of the effluent; about 18°C. Rate of perfusion; 50 to 60 ml. per minute. The cooling perfusions in the two

different routes were carried out; i. e. usual ventriculocisternal perfusion for the first two cases and the perfusion between both lateral ventricles for the last patient.

Table 4. Clinical Cases Undergoing the Cooling Ventricular Perfusion

Case No.	1	2	3
Name of Patient	T. S.	K.N.	Z.S.
Sex	Female	Male	Male
Age	9	17	12
Diagnosis	Oligophrenia	Obsessional Compulsive Neurosis	Epileptic Dementia
Chief Complaint	Distractibility, Disobedience & Violent Attacks	Violent Attacks	General convultion and Violent Attacks
Psychiatric Symptoms	Retention Defect, Hypoprosexia and Apathism	Labile Mood and Habit Disorders	Hypoprosexia and Euphoria
Neurological Findings	None of Remarkable Pathological Signs	Moter Disturbance in R. Leg and L. Extensor Plantal Reflex	Moter Aphasia
Effects after Perfusion	Become Docile and Bright	Alleviated from Violent Attacks	Alleviated from Epileptic Seizures

Table 5. Conditions and Physiological Changes During the Cooling Ventricular Perfusion in Clinical Cases

Case No.	1	2	3
Route of Perfusion	Post. Horn of L. Lat. Ventr. →Major Cistern	Post. Horn of L. Lat. Ventr. →Major Cistern	Ant. Horn of L. Lat. Ventr. →Ant. Horn of R. Lat. Ventr.
Times of Perfusion	3	9	2
Duration of Perfusion	4.5～10 min.	3～10.5 min	5 min.
Temp. of Influent	5.5～8°C.	5～12°C.	10°C.
Temp. of Effluent	18～26°C.	16～28°C.	20°C.
Rate of Perfusion	30～50ml/min.	80～120 ml/min.	50 ml/min.
State of Consciousness	Stupor	Stupor	Unchanged
EEG	Tendency to Low Voltage Slow Wave	Low Voltage	Spike Appeared
Respiration	Unchanged	Transient Apnea	Unchanged
Pulse Rate	Unchanged	Slightly Increased	Unchanged
Blood Pressure	Unchanged	Lowered	Unchanged
Muscle Tone	Relaxed	Relaxed	Relaxed
Incidents	None	Headache	None

In the first female infant, a case with mental debility, who had been remarkably insubordinate, the cooling perfusion under adequate conditions was performed.

She became stuporous in about several minutes after the beginning of the perfusion and completely recovered her consciousness after a lapse of 4 to 5 minutes from the time when the perfusion ceased. During and after the perfusion there were no changes in her respiration, pulse, blood pressure and body temperature; no convulsion throughout. After the cooling perfusion she became docile and bright.

In the second case, the cooling perfusion was so vigorously carried out that a transient apnea took place during the perfusion and he complained headache afterward. After the perfusion he was alleviated from the violent attacks.

In the last case, the aqueduct and the fourth ventricle were excluded from the route of perfusion, so that the effect of cooling was insufficient. His consciousness and other physiological conditions remained unchanged throughout the maneuver, while he became placid and was alleviated from the epileptic seizures.

DISCUSSION

According to the recent knowledge about the cerebral hypothermia, all of physiological conditions in the living body is to be reduced when the cerebral temperature is lowered at 15°C. to 20°C., corresponding as same grade as the condition at 30°C. of body temperature resulted from general hypothermia,[5)28)46)47)] From this view point in a local hypothermia of the central nervous system, our experiments on the cooling perfusion of the cerebral ventricular system were attempted to cool the thin layer of the nervous tissues close to the cerebral ventricles, which have more essential functions than the cerebral cortex for the maintainance of life, and to investigate the changes in the nervous functions during and after the cooling perfusion.

From the results obtained from the measurement of cerebral temperature in this experiments, remarkable reduction of temperature was observed in the areas being close to the ventricular wall, such as the medial thalamus, hypothalamus, periaqueductal grey matter and the floor of the fourth ventricle, when the unresponsiveness was obtained.

On the contrary, the reduction of temperature in the cerebral cortex and the subcortical tissues was slight, in contrast to the demonstrations by many investigators that the brain was the most conductible upon the thermal change than any other tissues.[17)18)] In fact, in the brain tissue being perfused constantly with warm blood flow the effect of hypothermia which invade a limitted area of the brain would not be considered to reach the remote areas within auch a short duration.

Analyzing the data obtained from these experiments, two concomitant factors should be taken into account; (1) mechanical stimuli against the ventricular wall

due to the pressure of perfsion, and (2) pharmacological action of electrolytes contained in the perfusate.

Although the ventricular wall was to be burdened considerably high pressure during the perfusion, control experiments with warm Ringer's solution revealed no harmful effects which was simply ascribed to either the mechanical stimuli against the ventricular wall or increased intraventricular pressure.

The cooling perfusion of the cerebral ventricles that brought about the reversible rapid unresponsiveness had no incidents so long as it was carried out up to 30 minutes. Temporary symptoms occasionally observed during and after the perfusion were seemed to be due to acute cerebral edema owing to the salt-action of the fluid, while electron microscopic study of the post-perfused brain revealed merely slight cerebral edema of the tissues close to the ventricular wall. Such symptoms as mydriasis, hypersalivation, acceleration of respiration, arrythmia, rigidity of muscles, convulsion, nystagmus, oculomotor palsy and exophthalmus were observed more frequently in the experiments with physiological saline than those with Ringer's solution. This discrepancy may be due to the difference of pharmacological effects of both fluids upon the nervous tissue.

It has been confirmed that the excitability of nervous cells increased when sodium ion abundantly invades into the cells, intracellular potassium ion is driven out. If a large amount of isotonic saline solution containing larger amount of sodium ion than cerebrospinal fluid comes into contact with the internal wall of cerebral ventricles, sodium ion accumulates so much in the cells that the central nervous cells are dehydrated, causing the accumulation of water in the brain matter. Consequently, these changes provoke severe incidents. HAYASHI[12] reported that the perfusion of the cerebrospinal fluid space with isotonic saline caused convulsion, which was designated as "salt discharge of nerve cell". Likewise, in the present experiments, convulsions were observed on the several cases perfused with physiological saline, though their frequency was not so high probably because of the brief duration of perfusion.

When Ringer's solution was employed, on the contrary, the incidents seldom occurred and recovered quickly if occurred, possibly from the reason that potassium ion in the Ringer had an action of declining the reflex-excitability, and calcium ion also had a cramp-inhibiting effect.

Another interesting results in relation to the salt action was that the size of pupils was reduced in the cooling perfusion with Ringer's solution whereas it enlarged with physiological saline. From the pharmacological standpoint, it may be due to the difference of salt action between both fluids. In short, it may be assumed that mydriasis takes place on account of the effect of sodium ion to the center of whether sympathetic or parasympathetic nerves. On the other hand, myosis observed in the cooling perfusion with Ringer's solution may be

merely due to the cooling effect because of that the change in the size of pupils was hardly observed in the control experiments with warm Ringer. Above all, though the mechanism of the changes in pupils could not be verified in this study, such assumption is available that the myosis in the cooling perfusion with Ringer's solution may not be a result of parasympathetic stimulation from the fact that the light reflex, of which center exists in the oculomotor nucleus, is seldom affected by the cooling perfusion.

Judging from the results of the control experiments, changes in respiration, pulse, and blood pressure are also thought to be due to the effects of cooling to the respiratory and vasomotoric centers.

As far as the unresponsiveness during the cooling perfusion is concerned, it is unlikely that the salt action of the perfusate is responsible for it, on the basis of the control experiments with warm Ringer. From the detailed data of cerebral temperature in agreement with above conclusion, the aquired unresponsiveness in the present experiments is considered to be ascribed in merely the effect of hypothermia among several factors.

In addition, from the results of the control experiments with hot fluid, it is apparent that the rise of brain temperature does not effect as simillar as the fall of it upon the physiological status of animals, since hot Ringer was hardly capable of initiating such depressing effect.

There is a well known principle that the nerve is first excited and later paralyzed by various stimuli. In the cooling ventricular perfusion activity of nervous centers may be reduced reversibly after being activated. In fact, some cases in this experiments showed an initial transient increased rate of respiration and pulse as well as blood pressure during cooling ventricular perfusion.

This particular attitude of the nervous center under the local hypothermia was also assumed to be applied to the temperature-regulatory center in the hypothalamus from the fact that an initial transient elevation of cerebral temperature was recognized within hypothalamic region in this experiment.

INOUE[17] observed that when a part of cerebral tissues was affected by sudden thermal change, the transient reverse influence of temperature took place in the deep cerebral tissues. From this observation, he concluded that the brain would perform certain thermal regulation to preserve its constant temperature against the thermal change from its circumstances.

Concerning the relation between cerebral temperature and respiration, TADA[48] reported some decisive observations in his study on the temperature of the brain in freezing course. In his study, even when the cortical temperature fell to 25°C. the reduction of respiration was not so remarkable. On the contrary, from our present data, it was ascertained that when the temperature in the periventricular region fell beneath 25°C., respiration rate reduced remarkably and

respiratory arrest was apt to occur in spite of slight reduction of cortical or subcortical temperature. Therefore, it may be assumed that the periventricular tissue, as the medulla involves the respiratory center, suffered an intense effect of hypothermia, neverthless its influence to the cortex is slight.

In addition, according to the fact that in this experiment the unresponsiveness forewent constantly to the change of respiration, anoxia or brain anemia may not be considered to be responsible for such alteration in responsiveness. Likewise, LOUGHEED[28] concluded that no anoxia took place in the cerebral tissue under general hypothermia from his experimental results in which no alteration in the lactate-pyruvate ratio in cerebral blood under such condition.

In the electroencephalographic study, basic EEG pattern did not show any changes during such unresponsive state unless an excessive cooling effect was given to the ventricular wall, in that instances low voltage slow activity followed by abolishment of EEG activity was noted probably because of secondary anoxia due to paralysis of the respiratory center.

LOUGHEED[28,29] and ROSOMOFF[44,45] studied the patho-physiological changes occuring within the brain under hypothermia and reported that the brain metabolism was reduced conspicuously in all phases; cerebral blood flow, cerebral oxygen consumption, cerebrospinal fluid pressure and brain volume etc. when body temperature fell beneath 30°C. On the other hand, under the localized hypothermia, like as the present experiment, the reduction of the brain metabolism would take place at least in the periventricular tissue, showing remarkable fall of temperature practically under such condition.

In view of the function in the nervous tissue, it is well known that the conductivity of peripheral nerves is reduced when it is encountered to cold. CHATFIELD[8] reported an incompetency on the conduction of stimulus at beneath 9°C. in the peripheral nerve. On the cranial nerve, likewise, NOELL and BRILL'S observation on the optic nerve showed the reduction of conductivity running parallel with the fall of temperature.[37] This reduction was noted in an arc involving several synapses with as same grade as single nerve fiber by them.

On the central nervous system it has been confirmed by several investigators [7,26,37,44] that the hypothermia effected to lower the conductivity of stimulus. According to these investigations, the fall of cerebral temperature resulted the gradual reduction of electrical activity of the brain, and the spontaneous electrical activity diminished at beneath 17°C. and 21°C. of cerebral temperature. Furthermore, FAY and SMITH[11] described in their clinical report concerning general hypothermia that all reflexes gradually weakened as hypothermia advanced, and disappeared at beneath 25°C. of body temperature, then the patient lost a response to speech and became "cold anethetized" in this stage.

In general hypothermia the fall of cortical temperature had been considered to contribute such interception on the central nervous system as mentioned above, while in the present experiment the subject of hypothermia has been concerned within the periventricular tissue without fall of temperature in the cortex. Therefore it will be permitted to consider that the interception is performed within a certain portion as far as where an impulse reaches to the cortex in the present experiment, if the depressed wakefulness and sleeping state is elucidated by "deafferentation" of the cortex as KLEITMAN and CAMILLE[22] and BREMER[6] have described.

However, EEG patterns showed any alteration which indicated such interception neither in the cortical area nor deep in the thalamus even if the responsiveness of animals was lost during the cooling perfusion, as long as respiration was normally maintained. In addition, response to the repetitive electrical stimuli in the intralaminar portion of the thalamus was also not diminished by the cooling perfusion. Only evidence which might endose such hypothesis was that the unresponsiveness was accompanied with the abolishment of bursts and myograms elicited by the nose pinching stimuli. That is highly suggestive of an interception of nervous transmission at anywhere in the reflex arc from the skin receptor to facial muscles involved.

The experimental results of the localizing cooling perfusions by several different routes conduct such possible conclusion that the lateral and fourth ventricles may have little significance on the acquired unresponsiveness. Accordingly, the critical areas participating in this unresponsiveness may be narrowed in the limitted extent about the ventricular wall involved the third ventricle and aqueduct of Sylvius, and in these latter areas there exist many important nuclei and ascending tracts by which consciousness or awaked state has been considered to be maintained, viz. the medial thalamus, hypothalamus and the periaqueductal grey matter etc.

As regards the medial thalamus, first, the intralaminar thalamic nuclei and the centre median, which are generally believed as the relay nuclei in the diffuse thalamic projection system, form the internal wall of the third ventricle, or lay in the position not far from its wall. MORISON and DEMPSY,[34] DROOGLEVER FORTUYN and STEPHENS,[10] and HUNTER and JASPER[15] concluded that the highest center which contribute the maintenance of wakefulness existed in these medial thalamic nuclei from their electrophysiological studies.

MORISON and DEMPSY[34] reported that the repetitive stimuli in the area centering the medial lemniscus of thalamus evoked 5-10 c/sec. spontaneous electrical activity on the extensive cortical areas, while the stimuli in other relay nuclei evoked potential only on the corresponding limitted cortical areas. From this experiment they postulated two systems of specific and non-specific projection.

Then the latter was taken worthy of notice by JASPER[20] designated as diffuse thalamic projection system. Among the medial thalamic nuclei, centre median was referred as the center propagating an impulse into the thalamus diffusely by MCLARDY.[33]

MAGOUN[31] also took notice of these nuclei together with the hypothalamus as ascending relay between the diffuse thalamic projection system to the cortex and the reticular activating system in the medial brain stem which was essential to the maintenance of consciousness or wakefulness by means of the collateral transmission of afferent stimuli from the long sensory pathway. In addition, there is the massa intermedia being considered as the center of sleep by HESS and others[13] in the third ventricle.

Then, in the hypothalamus many investigators have also believed the existence of the center of wakefulness. RANSON[43] observed the somnolence caused by hypothalamic lesion. INGRAM[16] also reached the same conclusion from his observation that the destruction of the hypothalamus resulted in a sleep and high voltage slow wave in EEG. Such as a considerable theory was supported by LINDSLEY and others,[27] that the consciousness might be maintained by means of the discharging of the hypothalamic activity to the cortex. Likewise, MURPHY and GELLHORN[35] suggested that the cortex was activated by the upward hypothalamo-cortical discharge in the waking state. And then, BERNHAUT et al.[4] described of EEG at the arousing response following affernt stimuli that an exciting change appeared not only in the cortex but in the hypothalamus.

From these observations it is clearly recognizable that the hypothalamus also plays an important role in the maintenance of wakefulness. In this regard, the fact that the conducting tracts from the hypothalamus to the medial thalamic nuclei is passing through the periventricular tissue according to KUHLENBECK[23] should be worthy of note.

Finally, periaqueductal grey matter in the brain stem has been also considered to be indispensable area for the maintenance of consciousness by BAILEY and DAVIS[3] and VON ECONOMO.[52] ARAKI,[1] likewise, came to a similar conclusion on the basis of the studies on the coma puncture by TAKETOMO and TODA[2] and the experiments on the nicotine injection into this critical area by YABUNO.[53]

In a word, it may be concluded that the periventricular tissue within a limit of the third ventricle and the aqueduct of Sylvius plays an important role for the maintenance of consciousness or wakefulness, for the reason that this area consists of the medial thalamus, hypothalamus, periaqueductal grey matter etc. and periventricular tissue connects these structures. Therefore, the mechanism of the alteration of responsiveness in the present experiment may be depended on the interception of neural function in these critical areas.

Precise experimental studies were followed by clinical application of this

technique in three psychiatric patients with violent behavior. Our expectation of the therapeutic attempt using this technique was based on the observation that violent dogs became docile after the cooling ventricular perfusion. In fact, as mentioned above, our expectation was fully rewarded with successful results. The patients with violent behavior became docile and severe epileptic seizures were subsided to such extent as being enabled to be controlled by anticonvulsant drugs postoperatively. For the therapeutic purpose, so far as controlling the epileptic seizures, our experience showed that the cooling perfusion of both lateral ventricles is effective enough with simplicity and safety in the technique of perfusion.

Since the first report of this study had been presented at the Second International Congress of Neurological Surgery at Washington D. C.,[50] further investigations were performed by several investigators using this technique. COSTAL and others[9] studied the same technique on dogs by various routes of flow and achieved the cerebral cortical temperature as low as 12.6°C. after a long duration of the perfusion. According to their study, the animals survived for long-term observation and the gross and microscopic studies of the brain from sacrificed animals otherwise were free of pathology, though the perfusion had been continued as long as 2 to 7 hours. OMMAYA and BALDWIN[39] employed this technique combined with cortical surface cooling as a therapeutic attempt in a case of myoclonic epilepsy following the precise experimental study on monkeys[38] in which the animal lost consciousness after 10 to 15 minutes of cooling and it returned with 15 to 20 minutes of cessation of cooling. They achieved the lowest temperature of effluent at 20° to 25°C. in their clinical case and status epilepticus was appeared to be disrupted.

From our meager clinical experiences, exact significance in the clinical effects of the cooling ventricular perfusion would not be confirmed, but certain therapeutic effects may be expected in the neurological and psychiatric disorders. Therefore, this technique is to be considered as a feasible and efficacious approach in the neurological clinic.

SUMMARY

Entire cerebral ventricular system was perfused with cold Ringer's solution on dogs from either side of the lateral ventricle to the cisterna magna. Under suitable condition for the perfusion dogs became unresponsive to the external stimuli after ten to thirty seconds of cooling. In the course of perfusion, respiration became slow and deep with a tendensy to slight bradycardia, and blood pressure was lowered, while rectal temperature remained unchanged throughout. With a lapse of ten to thirty seconds after the cessation of perfusion, dogs returned completely to their previous state, and acquired no pathological signs.

In the control experiments, dogs perfused with warm as well as hot Ringer under the same conditions did not show such unresponsive state and physiological changes. In the use of saline, however, convulsions and other pathological symptoms were recognized. Measurement of brain temperature during the cooling revealed that the decrease in temperature of the brain matter was remarkable and rapid in the thin layers under internal wall of perfused ventricles, especially in the hypothalamus and circumference of the aqueduct of Sylvius, whereas in the cortical and subcortical tissues the temperature remained almost equal to the body temperature.

From the results of the localized cooling perfusion by several routes of flow, the lateral and fourth ventricles might be dismissed from the essential mechanism of unresponsiveness which was elicited only when the third ventricle and the aqueduct was effectively cooled. In the electroencephalographic study, basic patterns of EEG activity were altered neither in the cortical area nor deep in the thalamus even if the responsiveness was lost under ventricular cooling. Intrathalamic responses to the repetitive electrical stimuli to the medial thalamus were not diminished under such condition. However, the responses on the EEG and EMG to the pinching animal's nose were completely abolished during such state of unresponsiveness.

Postoperatively dogs survived without any neurological defects or symptoms. Electron microscopical study of the postoperative brain demonstrated merely slight cerebral edema occurred in the periventricular tissue.

From these results, it is confirmed that the initiation of experimental unresponsiveness can be produced by the cooling perfusion of cerebral ventricular system under adequate conditions. As for such acquired unresponsiveness, only the hypothermic effect against the ventricular wall is possibly responsible for it. Accordingly, it is surmised that the interception of neuronal transmission on the thin layers under the internal wall of the third ventricle and aqueduct of Sylvius caused by the cooling may play an important role in this unresponsiveness.

Cooling ventricular perfusion was carried out on three psychiatric patients with violent behavior under a therapeutic expectation. After the maneuver, all of them became docile and epileptic seizures were subsided effectively. This technique is considered to be feasible and efficacious method as an attempt to treat unmanageable cases in the neurological and psychiatric clinic.

REFERENCES

1) ARAKI, C.: *Saishin-Igaku,* **8**: 1265, 1953.
2) ARAKI, C., TAKETOMO, T. and TODA, T.: *Acta schol. Med. Univ. Kioto,* **27**: 205, 1949.
3) BAILEY, P. and DAVIS, E.W.: *Abst. Arch. Neurol. & Psychiat.,* **53**: 325, 1945.
4) BERNHAUT, M., GELLHORN, E. and RASSMUSEN, A. T.: *J. Neurophysiol.,* **16**: 21, 1953.
5) BIGELOW, W. G. et al.: *Ann. Surg.,* **132**: 849, 1950.
6) BREMER, F.: *Soc. Ital. Biol. Sper.,* **13**: 271, 1938.
7) CALLAGHAN, J. C. et al.: *Ann. Surg.,* **68**: 208, 1954.
8) CHATFIELD, P. O.: *Am. J. Physiol.,* **155**: 179, 1948.
9) COSTAL, M., OWENS, G. and WOLDRING, S. J.: *J. Neurosurg.,* **20**: 112, 1963.
10) DROOGLEVER FORTUYN, J.: *EEG Clin. Neurophysiol.,* **3**: 393, 1951.
11) FAY, T. and SMITH, G. W.: *Arch. Neurol. Psychist.,* **45**: 215, 1941.
12) HAYASHI, T.: *Chemical Physiology of Exitation in Muscle and Nerve,* P. 139, Nakayamashoten Pub. Co., Tokyo, 1956.
13) HESS, R. J. R. ét al. : *EEG Clin. Neurophysiol.,* **5**: 75, 1953.
14) HIGASHI, K.: *Arch. Jap. Chir.,* **26**: 624, 1957.
15) HUNTER, J. and JASPER, H.: *EEG Clin. Neurophysiol.,* **1**: 305, 1949.
16) INGRAM, W. R. et al.: *EEG Clin. Neurophysiol.,* **3**: 27, 1951.
17) INOUE, B.: *J. Osaka Univ. Jap. Edition,* **7**: 433, 1955.
18) INOUE, B. and MAENO, S.: *J. Osaka Univ. Jap. Edition,* **7**: 647, 1955.
19) ISHII, S.: *Brain and Nerve,* **14**: 357, 1962.
20) JASPER, H.: *EEG Clin. Neurophysiol.,* **1**: 405, 1949.
21) KIMOTO, S., SUGIE, S. and ASANO, K.: *Clin. Surg.,* **10**: 293, 1955.
22) KLEITMAN, N. and CAMILLE, N.: *Am. J. Physiol.,* **100**: 474, 1932.
23) KUHLENBECK, H.: *Milit. Surg.,* **108**: 205, 1951.
24) LABORIT, H. and HUGUENARD, P.: *Press Med.,* **59**: 1329, 1951.
25) LEE, C. J. & BAKAY, L.: *Arch. Neurol.,* **13**: 48, 1965.
26) LIBET, B. et al.: *Am. J. Physiol.,* **129**: 404, 1940.
27) LINDSLEY, D. B. et al.: *EEG Clin. Neurophysiol.,* **2**: 483, 1950.
28) LOUGHEED, W. M. and KAHN, D. S.: *J. Neurosurg.,* **12**: 226, 1955.
29) LOUGHEED, W. M. et al.: *J. Neurosurg.,* **12**: 240, 1955.
30) LUSE, S. A. and HARIS, B.: *J. Neurosurg.,* **17**: 439, 1960.
31) MAGOUN, H. W.: *Physiol. Rev.,* **30**: 459, 1950.
32) MARK, V. H. et al.: *Science,* **134**: 1520, 1961.
33) MCLARDY, T.: *EEG Clin. Neurophysiol.,* **3**: 183, 1951.
34) MORISON, R. S. and DEMPSEY, F. W.: *Am. J. Physiol.,* **135**: 280, 1942.
35) MURPHY, J. P. and GELLHORN, E.: *J. Neurophysiol.,* **1**: 455, 1949.
36) NAKAMURA, T.: *Arch. Jap. Chir.,* **34**: 1395, 1965.
37) NOEL, W. K. and BRILL, S. A.: *Air Force School of Aviation Medicine Report* # 1. proj. # 21-1202-0003, P. 1-33, 1953. (cited by ROSOMOFF)
38) OMMAYA, A. K. and BALDWIN, M.: *Neurology,* **12**: 882, 1962.
39) OMMAYA, A. K. and BALDWIN, M.: *J. Neurosurg.,* **20**: 8, 1963.
40) PAPPENHEIMER, J. R. et al.: *Am. J. Physiol.,* **203**: 763, 1962.
41) PARKINS, W. M. et al.: *Ann. Surg.,* **140**: 284, 1954.
42) POLLAY, M. and DAVSON, H.: *Brain,* **86**: 137, 1963.
43) RANSON, E. W.: *Arch. Neurol. Psychiat.,* **41**: 1, 1939.
44) ROSOMOFF, H. L.: *Surgery,* **40**: 328, 1956.
45) ROSOMOFF, H. L. and HOLADAY, D. A.: *Am. J. Physiol.,* **179**: 85, 1954.
46) SAKAKIBARA, S. et al.: *Clin. Surg.,* **10**: 305, 1955.
47) SWAN, H. and ZEAVIN, L.: *Ann. Surg.,* **139**: 385, 1953.

48) TADA, N.: *Nisshin-Igaku,* **31**: 421, 1949.
49) TAKEUCHI, T. and MORITA, T.: *Brain and Nerve,* **9**: 45, 1957.
50) TOKUOKA, S., AOKI, H., HIGASHI, K. and TATEBAYASHI, K.: *IInd int. Congr. neurol. Surg.* (Washington, D. C., 1961). Excerpta med., No. 36, E148-E149, 1961.
51) UEDA, M. et al.: *J. Jap. Neurol. & Psychiat.,* **52**: 78, 1952.
52) VON ECONOMO, C.: *J. Nerv. Ment. Dis.,* **71**: 249, 1930.
53) YABUNO, S.: *Acta Scol. Med. Univ. Kioto,* **32**: 32, 1953.