Effect of Profound Hypothermia with Circulatory Arrest in Dogs

Special Reference to Changes in Cerebrovascular Permeability

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THE OBSERVATION of complications of the central nervous system, especially in children [6, 7, 9, 10, 20] following the use of profound hypothermia with circulatory arrest, has precipitated much experimental study of this technic to define the hazards and to observe associated physiologic changes.

Some experimental evidence suggests that the blood-brain barrier may be affected by deep hypothermia.[34] A relationship between the observed changes in the central nervous system and disruption of this barrier could exist. The present study was conducted primarily to determine the effect of profound hypothermia and circulatory arrest upon cerebral vascular permeability, brain morphology, the electroencephalogram and acid-base balance but secondarily to evaluate the effect of stasis alone, cold alone, or the formation of gaseous emboli in the cause of any resulting change.

Method

Mongrel dogs of 11–18 Kg. weight were used. Experiments were conducted using sterile technic. Two and one-half per cent pentothal sodium given intravenously was used for anesthesia. The lungs were inflated with oxygen by means of an automatic cycling device.

Various groups of control and determinate experiments were performed as follows:

1. *Control Circulatory Occlusion* (12 dogs). Dogs were subjected to complete temporary occlusion of cerebral circulation by intrathoracic clamping of the cavae (except the azygous), the aortic arch and brachiocephalic artery as described by Kaupp [27] for periods of 15–45 minutes to test the effect of stasis in cerebral blood flow and anoxia alone upon cerebral vascular permeability without the added factor of hypothermia. Animals were heparinized. Upon release of the occlusion, sodium fluorescein in 20 per cent solution (25 mg./Kg.) was injected intravenously and the dog was allowed to stabilize for 30 minutes. The animal was then sacrificed and the brain removed, sectioned coronally and the number and size of fluorescent areas counted under ultraviolet light using the method of Story and others.[40] The electroencephalograph (EEG) was monitored through frontal and occipital leads of an Edin Anesthograph. Aortic blood pressure and electrocardiogram were also monitored.

2. *Perfusion Controls at Normothermia* (18 dogs). These animals were perfused at normothermia for 60 minutes. A sternal splitting incision was used. In the perfusion circuit, similar to that of Drew's [19] (Fig. 1), blood was removed from the right atrium by gravity and pumped into the pulmonary artery through a plastic catheter inserted in the pulmonary outflow tract

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using the dog's own lungs as the oxygenator. Blood then flowed from the left atrium by gravity and was pumped through a Pemco heat exchanger, with bubble trap, to the femoral artery. Blood temperature was controlled by circulation of water of known variable temperature through the heat exchanger. Sigmamotor TMI pumps, calibrated by direct measurement of flow after each experiment, were used. Flow between the two systems was balanced by adjusting the pulmonary circuit pump. The system was primed with freshly drawn heparinized (20 mg./600 ml.) homologous blood. In addition, the experimental animal was heparinized using 1.5 mg./Kg.

A Walton-Brodie strain gauge arch was sewn to the right ventricle for measurement of the myocardial contractile force in many experiments. These observations will be reported separately. Aortic and central venous pressures and electroencephalogram were monitored and recorded intermittently on an electronic recorder. Temperatures of the esophagus, rectum and right ventricular chamber were routinely monitored by the insertion of thermistor probes.

Arterial and venous samples were drawn at the beginning, termination and 30 minutes after the perfusion for the determination of oxygen content, carbon dioxide content and pH. The oxygen and carbon dioxide content of whole blood was determined using the method of Van Slyke and Neill.[42] Plasma pCO_2 was estimated using the nomograms of Van Slyke and Sendroy.[43]

At the termination of the perfusion, blood volume was adjusted to stabilize the aortic and venous pressures within a normal range. Metaraminal bitartrate drip (10 mg./500 ml.) was occasionally used to support blood pressure. Animals were permitted to stabilize for 30 minutes prior to closure in survival experiments or sacrificed for the determination of cerebral vascular fluorescence. In the latter group, the sodium fluorescein was given intravenously

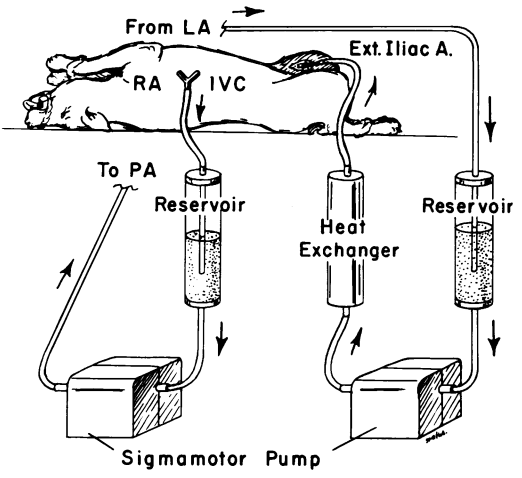

FIG. 1. The perfusion circuit. The dog's lungs served as the oxygenator.

60 minutes before sacrifice. Brains were studied for fluorescence as above. Animals in the survival group were observed and were sacrificed within 7 days. Brains were preserved in formal saline solution and subsequently processed for morphologic study. Changes attributable to artifacts associated with conventional methods of brain re-

TABLE 1. *Brain Fluorescence*

Group	No. Dogs	Duration of Arrest or Perfusion (min.)	No. Fluorescent Areas*
1. Cerebral circulatory occlusion	4	15	1/1 (0–4)
	5	30	5/1 (0–20)
	3	45	19/3 (0–38)
2. Normothermic perfusion controls	8	60	5/2 (0–19)
3. Hypothermic perfusion without circulatory arrest	6	60	22/5 (10–50)
4. Rapid cooling and warming without sustained period of hypothermia or arrest +	4	0	1/0 (0–2)

* Mean no. of areas less than 3 mm. diam./Mean no. of areas 3 mm. or more in diam.
( ) Range of no. of areas less than 3 mm. in diam.
+ One dog cooled only and sacrificed.

TABLE 2. *Summary of Data from Survival Experiments*

	Duration of Arrest of Perfusion (min.)	No. Dogs	Cooling Period* (min.)	Flow Rate* (ml./Kg)	Arterial pH* Pre / Post Perfusion	Arterial O_2 Saturation* (%)	Venous O_2 Saturation* (%)	Arterial pCO_2* (mm. Hg.)	Blood Pressure* (mm. Hg.)	Initial Arrest Temp. (°C.) Esoph. Card. Rectal*	End Arrest Temp. (°C.)*	Survived	Died	Neurologic Changes	Cause of Death
Normothermic perfusion controls	60	10	—	67	7.44 / 7.36	101 / 101	69 / 62	23 / 24	136 / 114	38 38 38	38	7	3	0	Atelecthasis & hemothorax —1 Rt. Ventric. arrest—1 Undetermined—1
Profound hypothermia with circulatory arrest	30	8	24	66	7.405 / 7.28	97 / 97	77 / 66	26 / 24	94 / 91	9 11 21	14 18 24	4	4	2	Hemothorax —2 Unknown—2
	45	8	27	70	7.39 / 7.21	96 / 96	78 / 69	26.2 / 28.1	87 / 94	9.1 9.6 17.6	15.5 15.6 20.4	2	6	4	Atelectasis & hemothorax —1 Rt. vent. failure—1 Hemothorax —1 Undetermined—3
	60	7	29	69	7.34 / 7.12	97 / 96	68 / 60	29 / 37	91 / 106	8.2 10.3 15	14.5 16 20.8	2	5	2	Hemothorax & atelectasis—3 Technical—1 Neurologic dis.—1
Profound hypothermia without circulatory arrest	60**	3	19	57	7.33 / 7.19	92 / 82	82 / 53	31.9 / 43.7	106 / 120	10 12 15	9 9 12	2	1	0	Subarachnoid hemorrhage —1 (day of op.)

* Mean values.
** Expired in 45 min. (1 dog).

TABLE 3. *Summary of Data from Groups Sacrificed for Brain Fluorescence*

Group	Duration of Arrest or Perfusion (min.)	No. Dogs	Flow Rate (ml./Kg)	Art. pH	Art. O_2 Sat. (%)	Venous O_2 Sat. (%)	Art. pCO_2 (mm. Hg)		Perf. Aortic Pressure (mm. Hg)	Initial Arrest Temp. (°C.) (Esoph.) (Cardiac) (Rectal)	End Arrest Temp. (°C.)	Post Perf. Aortic Pressure (mm. Hg)	Fluorescent Areas*
Normothermic perfusion controls	60	8	67	7.34	99	66	26.5	Pre perf.	111	38	37	108	5/2
				7.34	96	66	26.4	Post perf.					
Profound hypothermic perfusions without circulatory arrest	60	6	65	7.37	96	77	26.3	Pre perf.	96	5–14 (Range)	5–14 (Range)	118	22/5
				7.32	91	68	23	Post. perf.					
Profound hypothermia with circulatory arrest	30	5	71	7.40	98	62	26	Pre perf.	83	9	17	92	24/7
				7.24	93	58	30	Post perf.		10	17		
				7.13	95	—	47	30 min. post perf.		18	22		
	45	4	88	7.415	93	65	21.4	Pre perf.	92	9.2	14.5	52	24/6
				7.32	97	63	20.5	Post perf.		10.4	15.3		
				7.31	93	57	21.2	30 min. post perf.		16.9	21.3		
	60	5	66	7.41	98	67	24.4	Pre perf.	94	11.2	17.2	89	46/4
				7.17	97	63	29.8	Post perf.		10.1	16.8		
				—	—	—	—			19.3	24.4		
Profound hypothermia with circulatory arrest (with sodium bicarbonate)	60	7	68	7.39	95	63	24.2	Pre perf.	140	9.4	16	112	69/5*
				7.35	94	58	24	Post perf.		9.8	16.6		
				7.31	92	—	22.2	30 min. post perf.		18.4	24		

Mean values.
* Confluence values as 100.

TABLE 4. *Rapid Cooling and Warming without Sustained Period of Hypothermia*

	Cooling					Warming			
Dog No.	Flow (ml./ Kg.)	Cooling Period (min.)	Mean Blood Pressure (mm. Hg)	Bubbles	Lowest Esophageal Temperature (°C.)	Warming Period (min.)	Mean Blood Pressure (mm. Hg)	Bubbles	Brain Fluorescence
103*	72	17	160	+ early + late	9.5	—	—	—	1/0
104	70	30	140	0	8	25	160	++ early 0 late	2/0
114	74	30	80	+ early	10	25	80	0 early +++ mid +++ late	0/0
115	63	30	100	0	11	30	140	0	0/0

* Not warmed.

moval and fixation in early experiments led to the use of a modified Cammermeyer perfusion fixation [14] prior to brain removal in subsequent experiments (Table 5).

In subsequent experimental groups, the same general procedure used for the normothermia perfusion controls has been followed except for modifications which are described.

3. *Profound Hypothermia Without Circulatory Arrest* (9 dogs). Animals were quickly cooled by the circulation of ice water in the heat exchanger. After an esophageal temperature of 10° C. was attained, the temperature of the heat exchanger was controlled to maintain that temperature for the 60-minute perfusion. Flow rates during this period were the same or slightly lower than during the period of cooling. At the end of one hour of cold perfusion, sodium fluorescein was injected and the animal was warmed. Normothermia was usually achieved after 30 minutes, and the perfusion was then terminated. Animals were permitted to survive or were sacrificed 30 minutes after stabilization at normothermia.

4. *Rapid Cooling and Warming Without a Sustained Period of Hypothermia or Arrest* (4 dogs). Here the effect of cooling and warming the animal without an added sustained period of hypothermia was observed. The gradients between temperatures of the water jacket of the heat exchanger and blood entering the exchanger were maximum (4° C./38° C. cooling, 40° C./10° C. warming). Sodium fluorescein was given between cooling and warming phases. The remainder of the experiment was similar to that in the preceeding group.

5. *Profound Hypothermia for Measurement of Brain Temperature* (3 dogs). A thermister needle was inserted into the cerebral cortex in order to measure brain temperature and to correlate this with temperatures measured in other regions. Animals were sacrificed at the termination of the experiments and brains were not used for study.

6. *Profound Hypothermia with Circulatory Arrest* (44 dogs). Hypothermia was induced as in the previous groups. When esophageal temperature of 11° C. or less was attained, the pumps were stopped for periods of 30, 45 or 60 minutes.

After the period of arrest, warming was completed as in Group 3 above. Sodium fluorescein was injected at the beginning of the warming period in dogs to be sacrificed. In some of the dogs in which 60 minutes of arrest was used, sodium bicarbonate

was given to note the effect upon myocardial contractility after recovery.

The procedure for resuscitation or sacrifice was similar to previous groups. Surviving animals were observed and sacrificed 24–96 hours after perfusion.

Results

Cerebral Circulatory Occlusion. The number of fluorescent areas observed in these animals are shown in Table 1 and Figure 2 in comparison with other groups.

Starting 30 seconds to 1 minute after

TABLE 5. *Microscopic Brain Morphology*

Group	Duration of Perfusion or Arrest	No. Dogs	Survival Time (Hours)	Initial Esophageal Temperature °C. (Range)	Pathologic Change
Normothermia perfusion controls	60 min.	2	24	36.5–38	Neurones normal. A few glial fibers around vessels and between gray and white matter in cerebral cortex.
			24		No change.
			3		Scattered dark neurones with hyperemia and fresh hemorrhages of the meninges and white matter.
Profound hypothermic perfusion controls	60 min.	3	24	10–12.5	Swelling of neurones. Glial cell swelling with probable edema of white matter. Endothelial swelling.
			72		No significant changes.
			24		Swollen neurones and Purkinje's cells. Pale granule cells in cerebellum.
Profound hypothermia with circulatory arrest	30 min.	3	48	7.5–8	Swollen neurones and dark forms, proliferation glial nuclei, increase glial fibers cortex and white matter, edema white matter.
			72		Swelling Purkinje's cells, glial cells with regressive forms and fiber formation. Swelling of myelin sheaths.
			24		Swollen neurones and dark forms. Neurones intact, glial proliferation with regressive forms, edema white matter.
	45 min.	3	48	7.0–7.5	Neurones normal, some edema and fresh hemorrhages in white matter, hyperemia.
			96		Neurones normal, edema with perivascular clearing, astroglia proliferation, perivascular fat droplets in white matter.
			24		Neurones normal. Astroglial proliferation with pale and regressive forms, edema white matter.
	60 min.	3	48	6–7.5	Ganglion cell degeneration deeper layers, swollen Purkinje's cells, glial cell proliferation white matter without fiber formation, pale and dark glial nuclei.
			48		Swollen neurones, neuronophagia, edema white matter, glial proliferation, necrosis caudate nucleus, fresh hemorrhages white matter, endothelial proliferation.

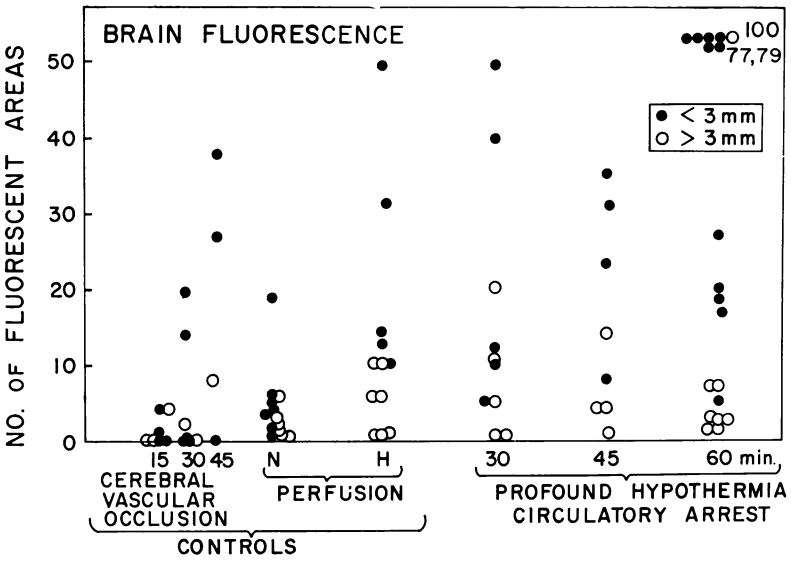

FIG. 2. Plot of number of brain fluorescent areas in control and circulatory arrest groups. Perfusion controls: N = normothermia, H = profound hypothermia without circulatory arrest. Confluent fluorescence given value of 100.

the vascular occlusion, all animals showed marked EEG depression which progressed rapidly to complete absence of activity. No EEG activity returned in any animal upon release of the clamps and re-establishment of circulation.

Normothermic Perfusion Controls. The data of 18 experiments are summarized in Fig. 2 and Tables 1, 2 and 3. Aortic blood pressure was maintained at adequate levels, the lowest recorded as 70–80 mm. Hg. Significant changes in venous pressure and EEG were not observed.

The fluorescent areas observed in controls may represent microemboli inherent in the perfusion system which could not be eliminated. Normal dogs, not perfused, do not demonstrate brain fluorescence in areas of brain studied.[36]

Hypothermia Without Circulatory Arrest. Observations in dogs subjected to profound hypothermic perfusion without circulatory arrest are plotted in Fig. 2 and tabulated in Tables 1–3. The average number of fluorescent areas, 22/5, shown in comparison with other groups in Table 1, is significantly higher than those of other perfusion groups without circulatory arrest.

Venous pressure showed no consistent change during these experiments even where retention of large amounts of blood was observed.

Evacuation of the bubble trap at intervals in four of the animals showed the accumulation of small numbers of fine bubbles during the cooling as well as the warming phase in three. One animal showed no bubbles. No correlation could be made between the observation of bubbles and brain fluorescence or neurologic signs.

The EEG in this group showed gradual slowing in rhythm and decreased in amplitude with frequent spikes as temperature fell. At 10° C. potentials were faintly visible but present during the perfusion. During warming, both rhythm and amplitude increased gradually and returned to precooling level at 34° C. (Fig. 3).

Rapid Cooling and Warming Without a Period of Prolonged Hypothermia. Data from experiments are shown in Tables 1 and 4. Although small numbers of microbubbles were observed during cooling and warming, there were no significant numbers of fluorescent areas in these animals in spite of the observations of few microbubbles.

Profound Hypothermia with Circulatory Arrest. Data from these experiments are summarized in Tables 2 and 3. Fluorescent areas are plotted in Figure 2.

Observations during the cooling phase of these experiments were similar to previously described groups. Temperature gradients at various sites during one experiment

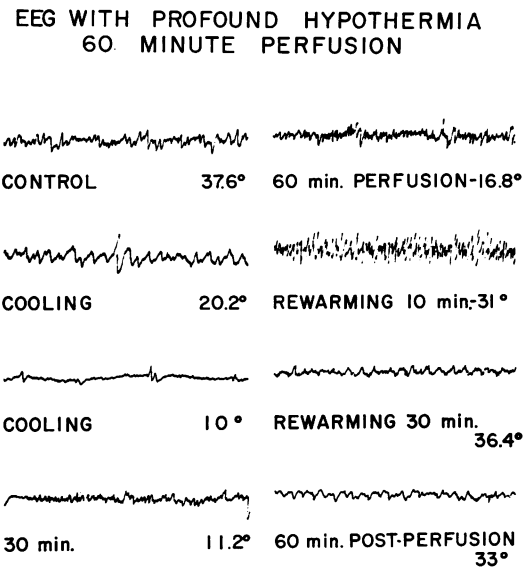

FIG. 3. Electroencephalograph during and following 60-min. profound hypothermia perfusion without circulatory arrest. Recovery is prompt upon warming.

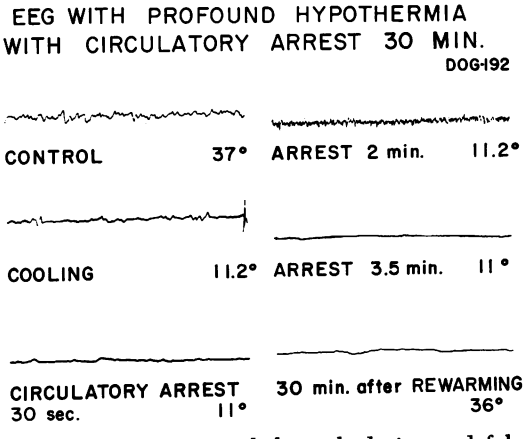

FIG. 4. Electroencephalograph during and following 30-min. period of circulatory arrest with profound hypothermia (11° C. esophageal temperature). There had been essentially no recovery 30 min. after the completion of warming.

are shown in Figure 5. The brain temperature followed most closely the temperature of the esophagus. The temperatures gradually drifted upward during the period of circulatory arrest, the rectal temperature rising less than the esophageal temperature. The greater rise in temperature in the 30-minute fluorescent arrest group probably related to the shorter cooling phase in that group.

Venous pressure was significantly elevated after perfusion in only one animal which succumbed in pulmonary edema after a 60-minute period of arrest.

Arterial and venous oxygen saturation and arterial pCO_2 at intervals following the perfusion were comparable to control values in 30, 45, and 60-minute arrest groups with few exceptions. The arterial pH did show significant decreases in post perfusion samples, and further decrease in subsequent 30-minute samples. The changes were most marked in the animals in which the period of circulatory arrest was longest.

The EEG pattern showed progressive decrease in amplitude and frequency of waves during cooling (Fig. 4); then the tracing became flat and remained so during the period of arrest. During warming, the EEG re-appeared at 20° C. in the 30-minute group and progressively increased but did not resume the previously observed amplitude and slow frequency even after normothermia was achieved. The EEG response in 45 and 60-minute arrest groups was variable. In most animals, little if any response was observed within the short postoperative period of observation. No correlation could be drawn between the number of fluorescent areas counted or the neurologic states in survival animals and the EEG response.

Brain fluorescence was significantly greater in these animals than in the groups perfused at normothermia or simply cooled and warmed (Fig. 2, Table 3). Confluent areas of fluorescence seen in many of the

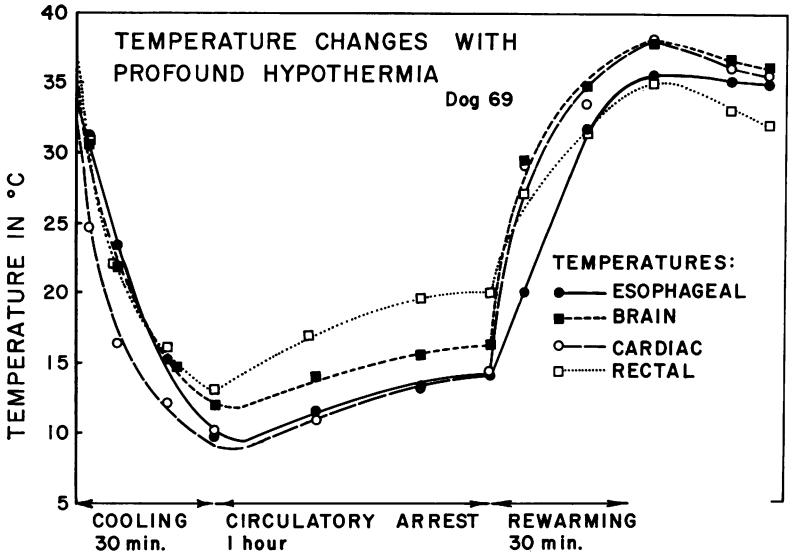

FIG. 5. Temperature gradients at various sites during experiment in which profound hypothermia with circulatory arrest was used.

60-minute arrest group were arbitrarily counted as 100-fluorescent areas. The presence or absence of microbubbles upon evacuation of the bubble trap showed no correlation with the number of fluorescent areas in the animals in which this observation was made.

The mortality rate in survival experiments was high. Many deaths were associated with findings of thoracic complications of hemothorax and atelectasis. Gross neurologic impairment, manifested by unsteadiness, hind limb paralysis or weakness, inability to stand, or foot drop, was observed in eight of the 13 animals which survived 24 hours or more.

Microscopic Morphology of Brains. Histologic study of 14 brains fixed by the perfusion technic confirmed the importance of this method of fixation, since the changes in the brains were not the same as those seen in the brains fixed in the ordinary manner with 10 per cent formalin-saline. The results are summarized in Table 5.

Only minor changes of neuronal swelling and chromatolysis, which were considered reversible, were seen with profound hypothermia without circulatory arrest and with arrest up to 45 minutes. The Purkinje's cells were especially affected. After 60 minutes of circulatory arrest, definite neuronal necrosis, edema and astrogliosis of white matter were observed (Fig. 6). Proliferation of endothelial vessels was seen in one animal and may be a direct reaction to endothelial injury by the hypothermia (Fig. 7).

Discussion

There is considerable controversy concerning the cause of neurologic changes after deep hypothermia and circulatory arrest. One study in rats even showed enhanced function of the brain after 120–150 minutes of suspended animation at 4° C.[26]

The many variables involved in both clinical and animal perfusions made the study of any one etiologic factor in changes of the central nervous system quite difficult. Some of the factors believed linked to the neurologic changes have been air embolism,[18, 28, 30, 39] hypoxia,[7, 29] sludged blood or formed element agglutination,[7, 8, 10, 31, 32] cerebral vascular constriction,[31, 35] rapidity [4, 15] and depth of cooling,[23, 24] rapidity of warming,[21] effect of cold *per se*,[3, 5, 6, 20, 22, 24] blood flow rate,[23, 24, 25, 37, 38, 44] cerebral vascular permeability changes,[2, 34, 39] affinity of

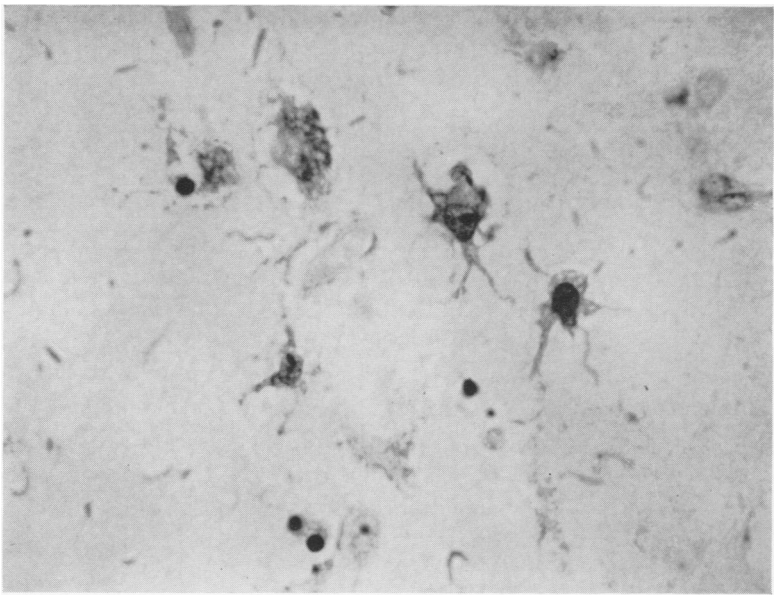

FIG. 6. Profound hypothermia with circulatory arrest for 60 min. and 48 hr. survival (Dog 162). Section of caudate nucleus showing severe necrosis of neurones, Nissl stain × 565.

hemoglobin for oxygen [13, 33, 41] and the duration of circulatory arrest.[23, 24]

Although the blood-brain barrier has been the subject of much investigation, its precise cellular location and mechanism is unknown. Most investigators identify the barrier with the capillary wall.[1] According to Bakay [1] the permeability is altered by physical changes only of extreme degree, and alterations of the barrier can hardly be effected by physiologic means. Broman [11] showed that solid emboli took hours to produce permeability changes but air emboli were followed by changes within minutes. Broman also indicated the defect in the barrier may be transient. That permeability changes may be reversible was also shown by Clemedson *et al.*[16] who produced

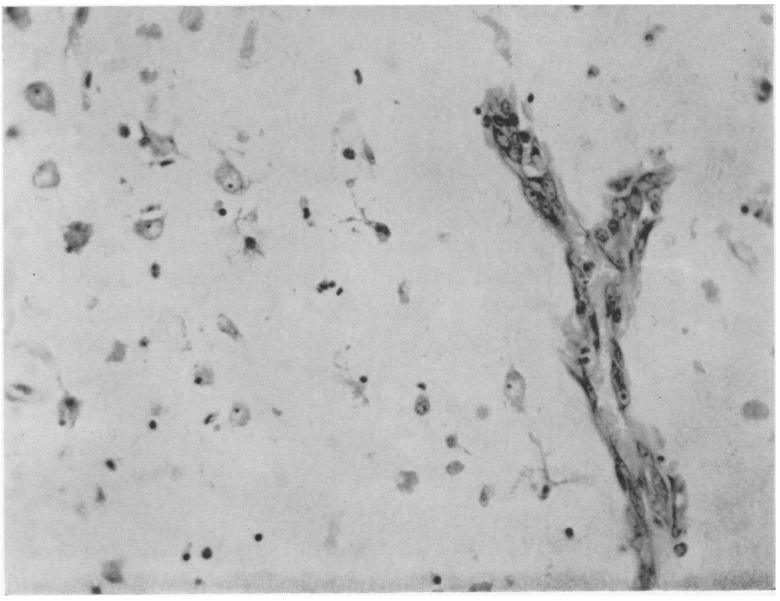

FIG. 7. Same dog as Fig. 6. Proliferation of vascular endothelial cells in caudate nucleus, Nissl stain × 235.

blood-brain barrier changes by the inhalation of 30 per cent CO_2 for 3 minutes in rabbits. Lourie *et al.*[34] studied the blood-brain barrier in animals with trypan blue after profound hypothermia. From that study, it appeared that the blood-brain barrier is partially disrupted at temperatures of 9° C. and below. Microscopic study of brains added little to their study.

Baldwin and others [2] studied the living brain under ultraviolet light after sodium fluorescein during total body perfusion at temperatures of 12–20° C. After 25 minutes of the cooling phase, the brain surface took on a fluorescent appearance which disappeared on warming. The fluorescence did not appear with perfusions at normothermia. Baldwin related the fluorescence to the maintenance of temperature between 20–23° C. for at least 26 minutes. He speculated that these changes may be relevant in the reports of clinical brain damage reported by others. The changes occurred even though 20 per cent Dextran was used in the priming mixture.

In the present study, the paucity of changes in fluorescence in the cerebral circulatory arrest group at normothermia, where significant neurologic impairment would be expected to result after a period of 14 minutes of cerebral vascular occlusion by this technic,[27] indicates that the blood-brain barrier is moderately resistant to hypoxia and stasis alone until a period of 45 minutes has elapsed, and even then changes are not always observed.

The finding of moderate fluorescence in the dogs subjected to prolonged hypothermic perfusion without circulatory arrest is evidence that the prolonged action of cold *per se* brings about some change in the blood-brain barrier and that complete circulatory arrest with the attendant stasis and hypoxia is not necessary for these changes to result. Also the relative resistance of the barrier to stasis and anoxia in the cerebral circulatory arrest controls at normothermia tends to discount these two factors alone as the causes. Since permeability changes were not seen when animals were rapidly cooled and warmed, the duration of cold appears to have importance as indicated by Baldwin.[2] It is possible that the intravascular fluid loss and hemoconcentration with subsequent aggregation of cellular elements occurs during this period. Increased blood viscosity and vascular constriction, which are known to occur with profound hypothermia, are other factors which may alter the cerebral vascular permeability.

There was good correlation between the duration of circulatory arrest, the severity of permeability change and the severity of nerve cell changes in the present study. This correlation and the absence of permeability changes after rapid cooling and warming, without prolonged period of hypothermia or circulatory arrest at moderate flow rates, are evidence against the relationship of the reported central nervous system changes and events which occur during the cooling and warming phases alone.

It is likely that the changes, believed irreversible, in blood-brain barrier and the neurones and astroglia observed after 60 minutes of circulatory arrest are not only the result of prolonged cold, previously noted, but also of excessive hypoxia whereby the tolerance of the brain has been exceeded. It is probable that anoxia was mostly responsible for necrosis of neurones after 60 minutes of arrest. It is not clear whether the endothelial proliferation observed in one dog was the result of hypoxia or hypothermia. Cerebral edema and perhaps neuronal swelling apparently can be produced by hypothermia alone.

The data showing the temperature drift upward during the period of circulatory arrest indicate that the safe time-temperature limits advocated by Gordon [23, 24] have been exceeded. Analysis of Bjork's report [7] of five cases with brain changes suggested

that this may have been an important etiologic factor in those patients.

In the present study, Purkinje's cells of the cerebellum were the most vulnerable. The swelling of neurones was ubiquitously distributed, not limited to zones especially susceptible to anoxia. Bjork found the caudate nucleus, globus pallidus, parietal cortex and hippocampus involved.[7] Hind limb paralysis has been observed by several investigators in dogs.[12, 29, 30] Connolly[17] observed decreased Purkinje's cells in dogs after selective brain cooling at 17–20° C., regardless of whether circulatory arrest was used.

Many investigators have attempted to define a safe period of circulatory arrest at normothermia and profound hypothermia. Methods of evaluation have been less sensitive than is desirable. The study of the effects of these methods upon psychomotor performance[45] and learned behavior[26] may reflect more subtle changes. Any given safe period will depend upon many variables which may affect other organs and systems. Many of the effects of profound hypothermia and circulatory arrest still remain unknown. Probably the most important limiting factor in profound hypothermia with circulatory arrest is availability of oxygen needed by the brain for its metabolism at the existing temperature.

Conclusions and Summary

1. Ninety dogs were subjected to complete cerebral circulatory arrest or profound hypothermia of 7–15° C., with and without complete circulatory arrest induced by extracorporeal circulation of moderate flow rates for periods of 30–60 minutes, in order to further elucidate the cause of reported changes in the central nervous system.

2. Cerebral vascular permeability was only mildly altered after 30 minutes of complete interruption of cerebral circulation at normothermia.

3. Profound hypothermic perfusion for 1 hour without circulatory arrest, or with circulatory arrest of 30–45 minutes, resulted in moderate changes in cerebral vascular permeability. When the circulation was interrupted for 1 hour, there was a significant increase in the number of fluorescent areas observed in the brain.

4. Minimal alteration of cerebral vascular permeability was observed in dogs perfused for 1 hour at normothermia or cooled rapidly and promptly warmed without a period of prolonged hypothermia or circulatory arrest.

5. Neurologic changes were observed in eight of 13 animals after 30 to 60 minutes of profound hypothermia and circulatory arrest.

6. Morphologic study of brains showed changes in neuroglia and ganglion cells and cerebral edema believed to be reversible if the period of circulatory arrest (initial esophageal temperature 6–8° C.) did not exceed 45 minutes. Severe irreversible ganglion cell changes were observed after 60 minutes of circulatory arrest. The severity of pathologic changes showed direct correlation with the severity of changes in the blood-brain barrier and the duration of circulatory arrest.

7. The electroencephalogram did not return to the precooling pattern in most animals after 30 or more minutes of circulatory arrest.

8. Decreases in blood pH were observed in animals after hypothermia, with or without circulatory arrest. Changes were most marked in animals subjected to 60 minutes of circulatory arrest and were believed to result partially from hypoxia attendant with circulatory arrest.

9. Although it was impossible by this study to separate all of the possible factors involved in central nervous system changes with deep hypothermia and circulatory arrest, the absence of significant changes in the blood-brain barrier after rapid cooling

and warming alone suggests that these changes may not be related to a) cerebral hypoxia during the cooling or warming phases alone, b) gas embolism, c) aggregation of formed elements due to cold alone during the cooling phase and d) the effect of cold blood entering the warm brain and warm blood entering the cold brain—etiologic mechanisms previously postulated by others.

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