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Experimental Studies of the Cerebral Tissue Oxygen Tension During Induced Systemic Hypotension and Intracranial Hypertension

by

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INTRODUCTION

Ischemic anoxia of the brain is one of the most important problems arising in many pathophysiological conditions of the central nervous system. Among many situations resulting in ischemic anoxia, systemic hypotension induced by blood deprivation and intracranial hypertension in particular were selected and the tissue oxygen tension of the brain was continuously determined and correlated with other parameters.

The principle, the application of and the limits of the polarographic measurement of tissue oxygen tension are also discussed.

1. MATERIALS AND METHODS

1) Experimental animals: about fifty mongrel dogs weighing 6 to 15 kg and unselected as to age and sex were used.

2) Anesthesia and preparation of the animal: each animal was anesthetized with intravenous pentobarbital sodium (nembutal) 30 mg/kg which was then supplemented as required. Endotracheal intubation was always performed. Respirators and succinylcholine chloride (s. c. c.) were used when required and non-rebreathing, volume- and pressure controlled respiration was maintained in the early series of experiments. A semiclosed infant circle coupled with pressure control (10 cm H_2O to -3 cm H_2O) was used in the later series of experiments. The animal was fixed on a modified HORSELEY-CLARK stereotaxic apparatus. Systemic blood pressure was continuously recorded with a strain gauge at the femoral artery. Other femoral vessels were also cannulated for blood sampling, blood withdrawal and transfusion. The common carotid and vertebral arteries were exposed bilaterally in the neck for occlusion experiments in one group of animals and to provide a route for formalin perfusion at the end of the experiment. A trephine hole was drilled into the left parietal bone, a rubber balloon was introduced into the extradural space towards the base of the brain, and the balloon was injected with 0.5 to 4 ml water to simulate an expanding intracranial lesion. A catheter from the femoral artery was introduced subdurally or intracerebrally in another group of animals to produce a hematoma. The bone defect was plugged with dental cement supplemented by muscle and skin sutures.

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A trephine hole was drilled in the midline at the vertex and a cannula was introduced for blood sampling into the superior sagittal sinus so that the tip of the cannula was near the confluens sinuum.

An indwelling needle was inserted into the cisterna magna and the cerebrospinal fluid pressure was recorded continuously.

In some animals, a small intracerebral balloon was introduced for recording the intracranial pressure contralateral to the expanding balloon.

The Beckmann pO_2 microelectrode about 1 mm in o. d. (outer diameter) was easily introduced into any intracranial region through a small trephine hole about 3 mm in diameter. However, at the end of the experiment, a piano-wire was inserted in the same place along the electrode and retained there until the exact position was revealed by autopsy.

A lefe subtemporal craniectomy was performed in some cases in which clips were placed on arteries of the circle of Willis.

The E. E. G. was monitored as required.

3) Apparatus, theory and application of the measurement of oxygen tension using microelectrodes.

Blood pressure, intracranial pressure, E. E. G. and E. C. G. were recorded with an 8-channel polygraph. The tissue oxygen tension of the brain was recorded with a BECKMANN physiological gas analyzer model 160 combined with pO_2 microelectrode which is an exact miniature of the Clark electrode.

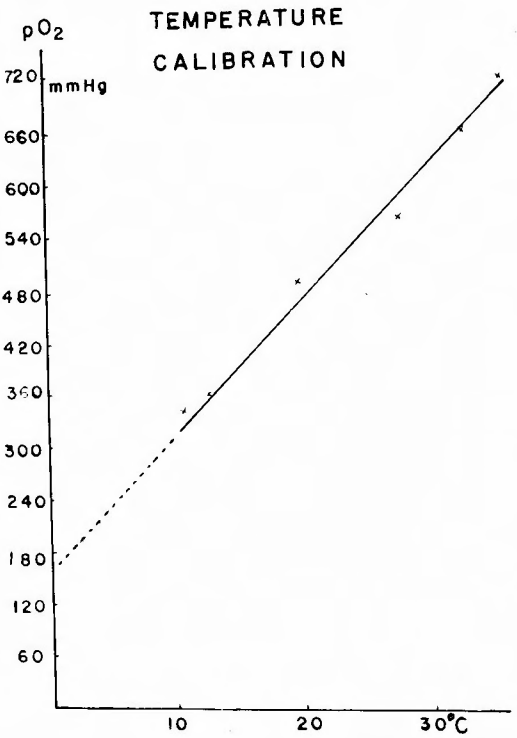

Fig. 1 : Temperature effect upon pO_2. The pO_2 decreases with the fall in temperature.

The measurement of oxygen tension by the polarographic principle was developed by DAVIES and BRINK as early as 1942 (6) and much progress has been made since then. However, many equivocal points have been left unexplored.

The Beckmann microelectrode is satisfactory in respect to both stability and reproducibility and calibration is easy with either gas or fluid. It can be inserted into any area of the brain, and even into larger vessels. The current increase and the temperature were in linear relation. The oxygen tension was elevated about 4% by a 1°C increase in temperature. The value obtained with gas calibration was 2.8% higher than with fluid calibration.

On the other hand, SUGIOKA and DAVIS[23] measured the oxygen tension of brain homogenate using the same type of electrode and found that differences among gas, supernatant and semiliquid tissue were less than 1% after equilibrium was established.

More than 90% of the response was attained in 30 seconds. When the electrode was inserted in brain substance, various pO_2 values were obtained depending on capillary density, the nature, number and size of nearby vessels and distance from the vessels.

The theoretical value of the tissue oxygen tension was calculated for the first time by KROGH[14] using a tissue cylinder model, but corrections have been made by further experiments and the theories of OPITZ, SCHNEIDER[21] and THEWS[24]. It is estimated to be between 17 and 100 mmHg depending on the exace place in the tissue cylinder. Is is higher on the arterial than on the venous side of the capillary and decreases at the periphery of the tissue cylinder which is supplied by a centrally situated capillary. 63 measurements performed on dogs are summarized in Table 1.

Measurements on human brain and spinal cord are shown in Table 2.

Table 1 dogs. 63 measurements

	Mean	Standard Deviation
Cerebral Surface	21.88 mmHg	17.99
Within cortex	33.33 mmHg	15.50
Deep in Brain substance	42.57 mmHg	29.80

Table 2 man

Surface of frontal cortex	20.0 mmHg	16.0 mmHg	17.0 mmHg		
Surface of spinal cord	16.0 mmHg	18.0 mmHg	20.0 mmHg	16.0 mmHg	16.0 mmHg

However, as my concern was to observe pO_2 shifts under various pathological conditions, high pO_2 points were sought to make the pO_2 changes more detectable and low values were dismissed through all the experiments. Thus, the mean pO_2 of simple measurements in the tissue might be lower than these figures.

Though the diffusion coefficient of steady diffusion was used in the calculation, much non-steady diffusion may occur in the living animal. The diffusion limiting vascular wall was not considered in the calculation. The theoretical value may be lower when these points are considered. The Beckmann microdelectrode measures the mean value of several points in the tissue cylinders and naturally many different oxygen tensions might be obtained depending on the area of insertion. Therefore, a comparison between the absolute values among different places is not reasonable.

The electrode also should not be moved during one experiment. These limitations made measurements with inserted electrodes more difficult than those with surface electrodes but not so difficult as with intracellular electrodes, as the object of study was diffusible oxygen. Bleeding and tissue destruction around the electrode form a diffusion layer having a uniformly distributed oxygen tension, which behaves as a transmitting medium of oxygen between the tissue and the electrode. The polyethylene or teflon membrane on the suface of the electrode behaves as a diffusion limiting factor because of its low diffusion coefficient. The reading of the oxygen tension does not change even if the position of the electrode shifts a little, as long as the electrode is in this diffusion layer of destroyed tissue.

However, when the impingement was enough to expel the electrode out of the diffusion layer, measurement became impossible. Care should be taken to keep the electrode and the brain untoughed after the electrode has been inserted into the right place.

Respiratory changes affecting the current reading were observed on several occasions but not in all. The inserted electrode reflects oxygen and nitrogen inhalation, asphyxia, blood pressure changes, vascular occlusion and ischemia due to increased intracranial pressure and is as reliable as the surface electrode, though difficulties may be anticipated in clinical use.

Calibrations were made in both the gas and liquid phases using oxygen, nitrogen and air in a cuvette system with a thermostat to maintain a constant temperature of 36°C.

Changes in oxygen tension in response to changes in blood pressure appeared in less than 2 minutes and were stable in 8 to 13 minutes. If no change was detected within 2 minutes after the specific condition was applied, it was considered to be stable. Changing values were followed from 8 to 13 minutes, and the next steps were never started until the reading became stable.

Temperature corrections were not made because the cerebral temperature of the animal was 35° to 36°C throughout the experiment and did not decrease conspicuously unless cardiac decompensation developed.

2. RESULTS

A. PRELIMINARY EXPERIMENTS

1) Oxygen tension of the blood measured in vivo.

Normal oxygen tension of the blood measured in vivo is shown in Table 3. Arterial pO_2 was maintained nearly constant with a mean of 93.6 mmHg oscillating at a mean amplitude of 11.8 mmHg in the steady state.

Table 3

		Arterial pO_2	Mean	Amplitude
Case 1	Exp. 1	72- 94 mmHg	83 mmHg	22 mmHg
	Exp. 2	108-112	110	4
	Exp. 3	92-110	101	18
Case 2		77- 84	80.5	3.5
Mean			93.6	11.8
Venous pO_2		50- 72 mmHg	61.0 mmHg	22.0 mmHg

Venous pO_2 was, though measured in only one case, also oscillatory. The mean was 61.0 mmHg and the amplitude of oscillation was 22 mmHg.

During oxygen inhalation the arterial pO_2 rose steeply to a peak of 285 mmHg in 3 to 4 minutes and returned to the original level in 5 minutes after air breathing.

During apnea induced by s. c. c. injection, the arterial pO_2 decreased to 17.2 mmHg two minutes and a half after the injection and increased to a peak of 470 mmHg following artificial respiration with oxygen. This is higher than after spontaneous respiration

with oxygen.

The rates of increase in arterial pO_2, cortical surface pO_2 and intracerebral pO_2 after oxygen inhalation are compared in Table 4. Each value increased to 2 to 6 times the original value after oxygen inhalation.

During systemic hypotension produced by blood withdrawal, the oxygen tension of the arterial blood was correlated with the tissue pO_2 as is shown in Table 5. The decrease of tissue pO_2 during extreme hypotension such as 40 mmHg systolic, may be caused not only by ischemic anoxia alone but also by concomitant anoxic anoxia due to ineffective oxygenation of the blood through the lungs.

Table 4 The Rate of pO_2 Increase after O_2 Inhalation

	Arterial pO_2	Cerebral Surface	Within Brain
1	285/80.5 mmHg (356%)	125/62 mmHg (202%)	250/25 mmHg (416%)
2	470/80 mmHg (590%)	115/42 mmHg (774%)	

Table 5

Arterial pO_2	Blood Pressure	Tissue pO_2 (Medulla)
112.0 mmHg	90 mmHg	18.0 mmHg
112.8	70	15.0
41.2	40	12.5

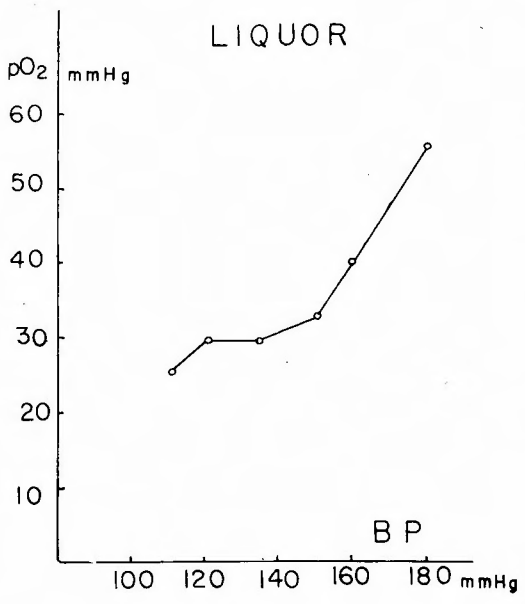

Fig. 2 : Systemic hypotension and pO_2 level of the cerebrospinal fluid measured in cisterna magna. The pO_2 fell with the descent of blood pressure.

2) Oxygen tension of the cerebrospinal fluid during blood pressure changes.

The pO_2 was measured continuously through a cisternally inserted electrode. The original value was 57 mmHg in case 1 and 55 mmHg in case 2. It was lower than the mean arterial pO_2 and close to the venous pO_2. The cerebrospinal fluid pO_2 varied promptly in less than 1 min. in direct proportion to the change in blood pressure, and a linear relationship with the blood pressure was demonstrated during systemic hypotension. As the cerebral blood flow is well known to be related to blood pressure, the pO_2 of the cerebrospinal fluid may be considered to reflect the whole cerebral blood flow.

3) Effect of ether anesthesia on cerebral tissue oxygen tension.

The initial value was 50.0 mmHg and rose to 65 mmHg when the level of anesthesia

was shallow and the animal began to move. It decreased to a minimum value of 6.0 mmHg when the level of anesthesia was extremely deep and recovered to 36 mmHg when the ether was shut off. The cerebral tissue pO_2 was considered to be in parallel relation to the depth of anesthesia.

4) Cerebral oxygen tension after administration of various agents.

a) The cerebral tissue pO_2 was observed to rise after the intravenous injection of cytochrome C. Similar tendencies were observed in two experiments.

b) After the intravenous injection of 1 mg/kg (half the lethal dose) of KCN, the venous pO_2 of the brain rose remarkably. Whether this was caused by depressed metabolism due to histotoxic anoxia or by increased blood flow could not be determined, as the blood pressure was elevated at the same time.

c) KCN drip. When KCN (2 mg/cc) was allowed to drip around the electrode onto the cortical surface in the first experiment, the tissue pO_2 increased initially followed by a small decrease and showed a stepwise increase after repeated dripping. However, in the next experiment no change was observed after dripping. In the third experiment in which KCN was injected into the brain substance immediately under the electrode, the surface pO_2 showed an initial decrease followed by a slight increase and reached a stable value lower than the original. In summary, no particular tendency was observed after KCN dripping in these experiments.

d) Epinephrine drip. Though some cases were reported in which cortical pO_2 did not change perceptively after the dripping of vasopressor drugs, the pO_2 of the cortical surface in this experiment decreased from an original level of 50 mmHg to 22 mmHg or 44% of the original, after the dripping of 0.1% epinephrine. This may be interpreted to indicate the grade of vascular constriction.

B. CEREBRAL OXYGEN TENSION AFTER LIGATION OF CERVICAL ARTERIES

1) Occlusion of the common carotid and vertebral arteries.

In 11 experiments performed on 3 animals the common carotid and vertebral arteries were occluded bilaterally in different sequences with no demonstrable effect on the tissue pO_2 of the cerebrum, cerebellum, medulla oblongata or pons. The vascular supply under these circumstances was interpreted to be perfectly compensated through the elevated blood pressure and rich collateral circulation.

2) Ligation of the cervical arteries and of the Circle of WILLIS. (Fig. 3)

In the first experiment, clips were placed at the origin of the left anterior cerebral artery and the posterior communicating artery and the change in pO_2 of the cerebral tissue in the area supplied by the middle cerebral artery was determined during ligation of the cervical arteries.

PO_2 was reduced to 85% after occlusion of the left common carotid artery and to 35% during bilateral occlusion of the common carotids followed by gradual recovery to 81%. The original value was regained after release. Occlusion of the right common carotid alone caused no change.

These findings seem to indicate that occlusion of the cervical arteries causes pO_2

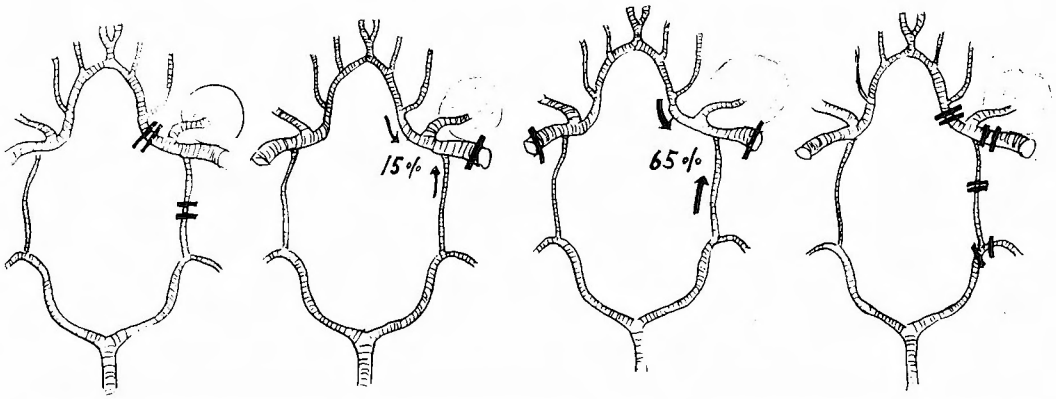

Fig. 3 : Ligation of the cervical arteries and of the Circle of Willis. The cortical pO_2 supplied by the Circle of Willis was 15% during unilateral common carotid ligation and increased to 65% after bilateral ligation.

decrease if there is an associated occlusion of the collateral circulation through the Circle of WILLIS, i. e., during occlusion of one common carotid artery, 15% of the cortical pO_2 is supplied through the collateral circulation via the Circle of WILLIS ; and during occlusion of both common carotids 65% of the cortical pO_2 is supplied via the Circle of WILLIS.

The remaining 35% of the cortical pO_2 is supplied via other collaterals (e. g. leptomeningeal), which can raise it to as much as 81%, due probably to a compensatory mechanism.

In the second experiment, clips were placed on left anterior cerebral artery, left middle cerebral artery, left posterior cerebral artery and left posterior communicating attery, followed by successive occlusion of the cervical arteries. The pO_2 of the left parietal cortex was reduced to 50% after left vertebral occlusion alone. Occlusion of the other vessels had no effect. The same results were obtained with different sequences of occlusion. 50% of the pO_2 of the left parietal cortex was considered to be supplied via collateral circulation other than the Circle of WILLIS ; from the right vertebral artery in this case.

The initial systemic blood pressure of 120 mmHg rose to 210 mmHg during complete occlusion of the cervical arteries and returned to its original level after release.

All these experiments are interpreted as follows. The blood supply to the brain of the dog is perfectly compensated during complete occlusion in the neck by elevation of the blood pressure and by collateral circulation which is differently developed in each case. The cortical pO_2 supplied by the Circle of WILLIS was 15% during unilateral common carotid ligation and increased to 65% after bilateral ligation.

Collateral circulation other than the Circle of WILLIS (e. g. leptomeningeal), supplied the remaining 35% of cortical pO_2 which could be increased to 81% in due time.

These figures in themselves do not represent blood flow but indicate the importance of the Circle of WILLIS in vascular occlusions of the neck.

C. THE CEREBRAL OXYGEN TENSIONS DURING INDUCED SYSTEMIC HYPOTENSION

The relationship between the degree of reduction of blood volume and the blood pressure is illustrated in Fig. 4.

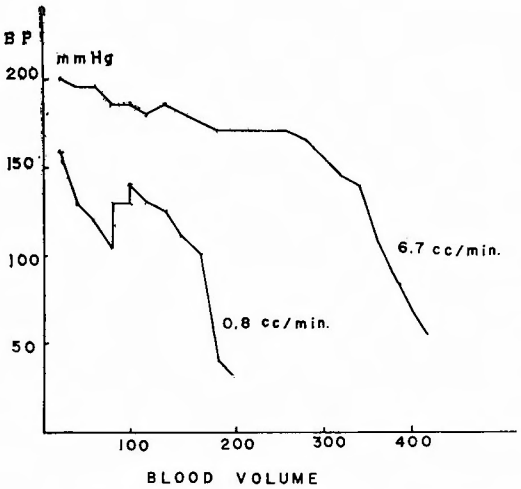

Fig. 4 : Slow and rapid withdrawal are compared.

With a slow rate of blood withdrawal (lower line), the curve of decrease of the blood pressure was interrupted by cardiovascular compensation and an elevation of blood pressure was observed despite continued steady blood deprivation. Thus the same blood pressure was obtained before and during the course of blood withdrawal. However, these two points should not be treated equally. Consequently rapid withdrawal (upper line) was employed until the required blood pressure was obtained without consideration of the volume of blood removed, to avoid confusion.

The oxygen tensions in the tissue and in the veins of the brain are plotted against the decreasing systemic blood pressure in Fig. 5 and in Fig. 6.

As is illustrated in these figures, a steep decrease in cerebral oxygen was noted at systolic blood pressures of 60 to 80 mmHg during blood deprivation, and pO_2 fell to 70% or lower of the original value. Below this critical level irreversible brain damage may

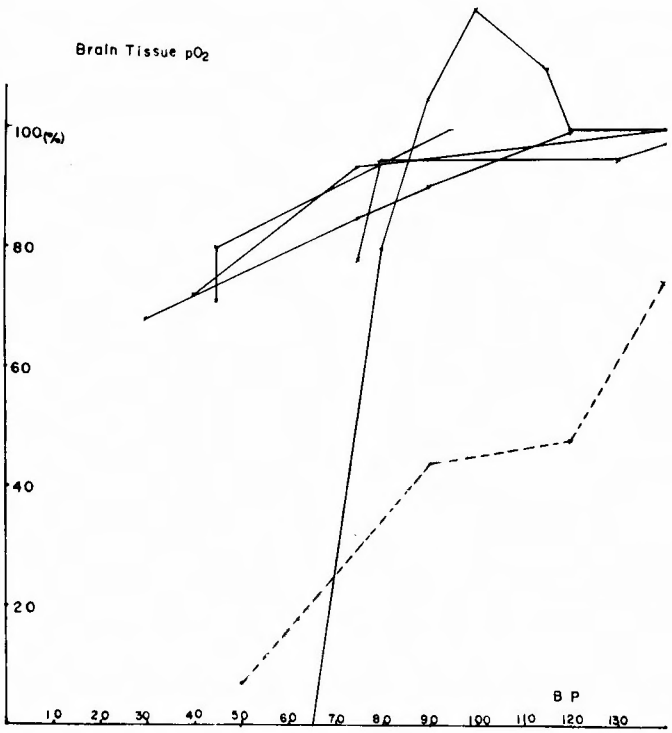

Fig. 5 : Systemic hypotension and cerebral tissue pO_2

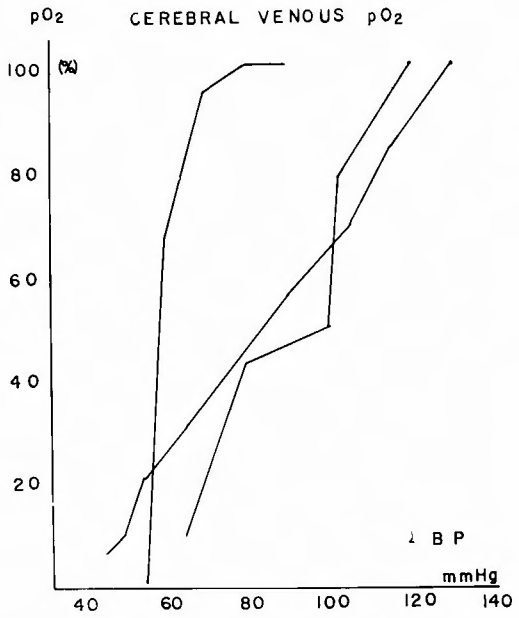

Fig. 6 : Systemic hypotension and cerebral venous pO_2.

develop.

Venous oxygen tension of the brain, on the other hand, decreased almost linearly with the descent of blood pressure and reached nearly zero at systolic blood pressures of 55 to 70 mmHg.

These results indicate that the blood oxygen was entirely absorbed into the brain at these blood pressures simultaneously with the beginning steep decrease of tissue pO_2.

Accordingly, a pO_2 of 70% and systolic blood pressure of 55 to 70mmHg were defined as critical levels below which irreversible damage should be anticipated. Irreversible damage of the medulla oblongata leads to the death of the animal. The E. E. G. monitored during these situations did not demonstrate marked change except for paroxysmal bursts of waves which were frequently observed during anoxia and believed to be due to

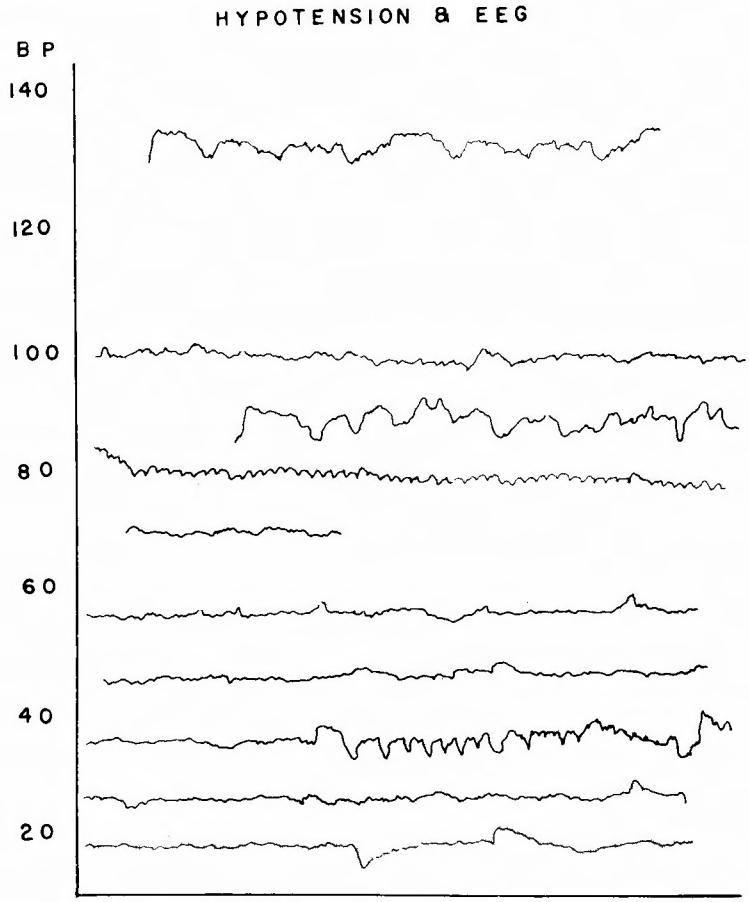

Fig. 7 : Systemic hypotension and electroencephalogram.

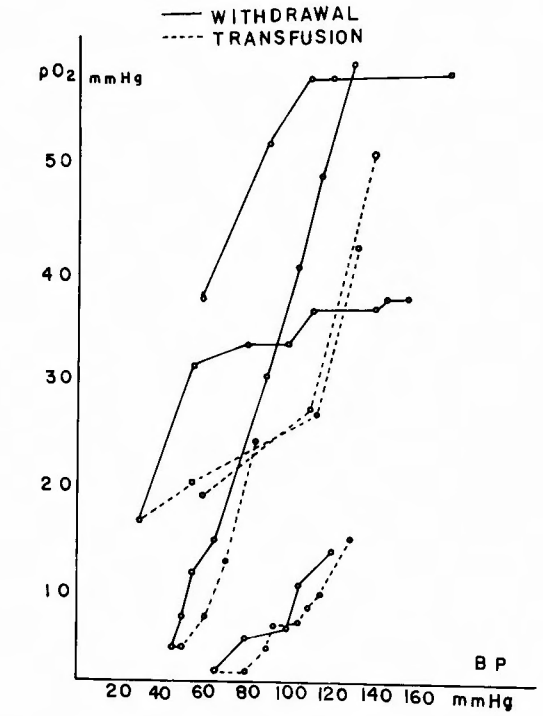

Fig. 8 : pO_2 during blood withdrawal and transfusion. pO_2 recovers with the rise in blood pressure.

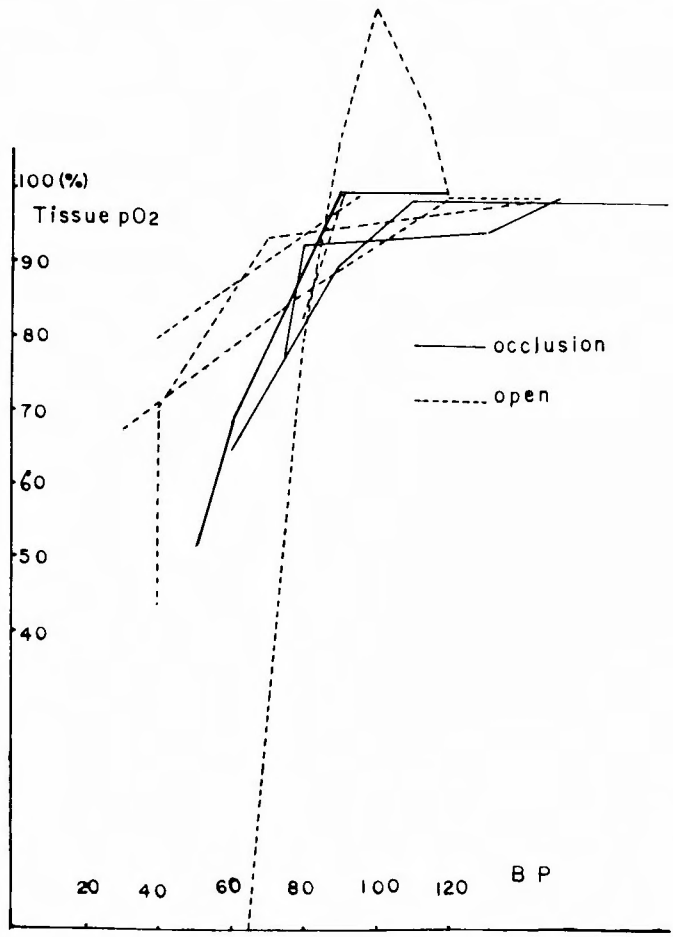

Fig. 9 : Cerebral tissue pO_2 during systemic hypotension compared between the group with occluded cervical vessels and the control. The pO_2 of the occluded group falls already at higher blood pressure.

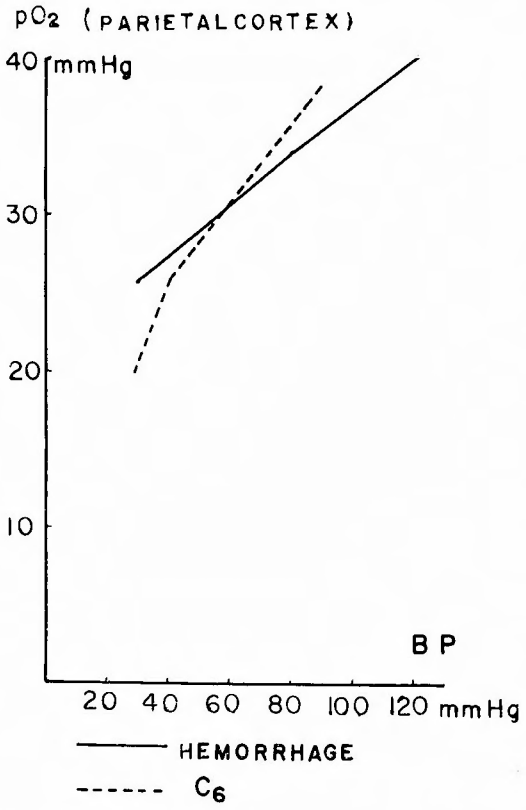

Fig. 10 : pO_2 descent was steeper after hexamethonium injection than during hemorrhage.

anoxia (Fig. 7).

After 8 to 13 minutes of exposure to oxygen tension below 70% of the original (i. e., below the critical level), about half the animals died despite blood transfusion. In the remaining half, the venous pO_2 and the tissue pO_2 recovered as the blood pressure rode (fig. 8). During transfusion a higher blood pressure than that corresponding to a certain pO_2 level during blood deprivation was required to restore the pO_2 to the same level. This is clinically important.

If the pre-shock level were 90 mmHg, restoration of blood pressure to 90 mmHg does not yet permit security because the pO_2 will not return to its original level until a higher pressure is obtained. The vascular resistance of the brain is believed to rise once the blood pressure is reduced, and the blood flow to the brain cannot be increased very easily under these conditions.

The effect of occlusion of the cervical vessels is illustrated in fig. 9. In the occluded group a steep fall in tissue pO_2 was observed when the systolic blood pressufe fell to 90 mmHg, which was 20 mmHg higher than the critical level in the controls. This observation indicates that during ligation of the cervical vessels, the blood flow to the brain reaches it via collateral circulations which fail at comparatively high blood pressure of 90 mmHg and the pO_2 of the brain is greatly reduced. These experimental results explain the clinical observation that patients with occluded cervical arteries often have cerebral ischemia even when their blood pressure is higher than shock level.

The cerebral pO_2 during the hypotension induced by hexamethonium and that caused by blood withdrawal are compared in Fig. 10. A steeper descent of pO_2 was observed in nervous shock (through C_6 injection) than in hemorrhagic shock. The decrease of pO_2 was greater in the former during the same degree of fall in blood pressure. Both pO_2 and blood pressure were more repidly restored by the injection of pressor agents than by blood transfusion.

D. CHANGES IN LOCAL OXYGEN TENSION IN VARIOUS AREAS OF THE BRAIN DURING INTRACRANIAL HYPERTENSION

1) Intracranial hypertension caused by balloon expansion.

Intracranial hypertension was produced by the injection of 2 to 4 ml of saline into a

balloon inserted epidurally, and the tissue oxygen tension, systemic blood pressure, cisternal pressure and balloon pressure were measured.

Intracranial hypertension produces increased vascular resistance and venous stasis resulting in cerebral ischemia. When the intracranial pressure exceeds a certain level, cerebral ischemia triggers a compensatory mechanism of pressor response to maintain effective blood flow, the so called CUSHING-phenomenon. The grade of ischemia or ischemic anoxia was investigated in various regions within the brain by the Beckmann-microelectrode inserted through a small trephine hole 2 mm in diameter.

The changes of oxygen tension varied greatly in different parts of the brain during the ischemia produced by increased intracranial pressure. The ischemic anoxia or the oxygen tension at which the CUSHING-phenomenon just began to develop in several regions are listed in Table 6. Note that the decrease of pO_2 was less in the medulla oblongata than in other regions and was higher in the cerebral cortex, mesencephalon and diencephalon. These results indicate that the elevation of blood pressure of the CUSHING-phenomenon, hitherto attributed to medullary ischemia, is in fact triggered from other more anoxic supretentorial areas such as the cerebral cortex, diencephalon or mesencephalon.

Table 6 Vasopressor Response and Per cent Decrease of Tissue pO_2

Medulla	72%	Cerebral Cortex	30%
〃	57	〃	96
〃	56	〃	18
〃	100	〃	0
〃	41	Mesenechalon	7
〃	77	〃	34
〃	90	Diencephalon	54
〃	88	Mean	34.1
〃	100		
〃	55		
〃	71		
〃	88		
Mean	74.6		

Continuously monitored oxygen tension, blood pressure, cisternal pressure or balloon pressure are illustrated in figs. 11 through 15. Vasopressor responses during ischemic anoxia by compression and restoration after decompression are prominent.

2) Anoxia during the formation of edema after compression.

The edema formation accompanying intracranial expanding lesion is widely known. The main cause of edema formation has been attributed to brain anoxia, or to disruption of the bloodbrain-barrier or to vasomotor paralysis. However, the true mechanism has never been exactly known. The auther analyzed cerebral anoxia continuously during and after balloon compression until the secondary elevation of intracranial pressure or edema formation were completed.

The normal cisternal pressure of the 17 dogs, in prone position and fixed to the modified Horseley-Clark stereotaxic apparatus, averaged 13.9 mmHg (189 mmH_2O), the S. D. being 8.9 mmHg. This pressure was raised to 30-80 mmHg (410 to 1000 mmH_2O) by compression. The compression was maintanied throughout the experiment, though in a few cases the saline in the balloon was partially removed after 2 to 4 hours of compression. As is shown in figs 16, 17 and 18, the pO_2 of the parietal cortex contralateral to the side of compression decreased to 40 to 50% of the original level, and the anoxia was maintained for 3 to 5 hours. This anoxia is considered to be related to edema formation. However, in one case as is shown in Fig. 19, edema failed to occur despite the

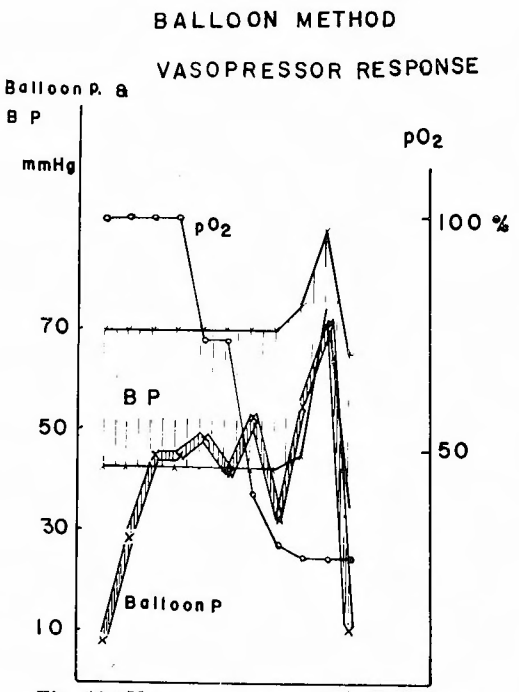

Fig. 11 : Vasopressor response and pO_2 in intracranial hypertension induced by the balloon method. Blood pressure remained unchanged at balloon pressure below 50 mmHg (680 mm H_2O) though the cortical pO_2 was already reduced to 71%. When the balloon pressure reached 55 mmHg (750 mmH_2O), the vasopressor response or Cushing's Phenomenon was evoked. Cortical pO_2 was reduced to 27%. Balloon p. and BP represent the balloon pressure and the blood pressure.

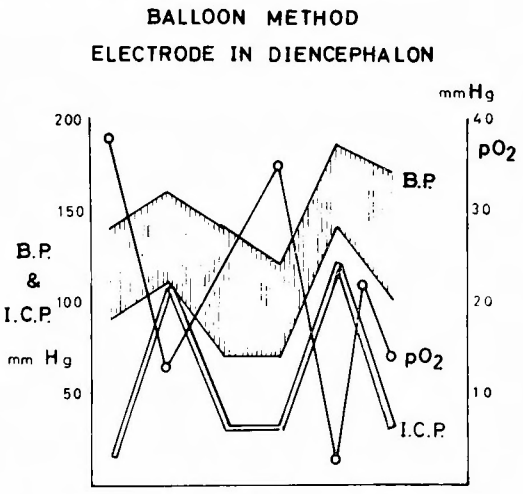

Fig. 12 : With a balloon pressure of 107mmHg (1460 mmH_2O), the pO_2 decreased to 34% and was restored to 92% when the pressure was lowered to 30 mmHg (400 mmH_2O). The balloon pressure was again raised to 120mmHg (1630 mmH_2O) with the descent of pO_2 to 8%. I. C. P. represents intracranial pressure.

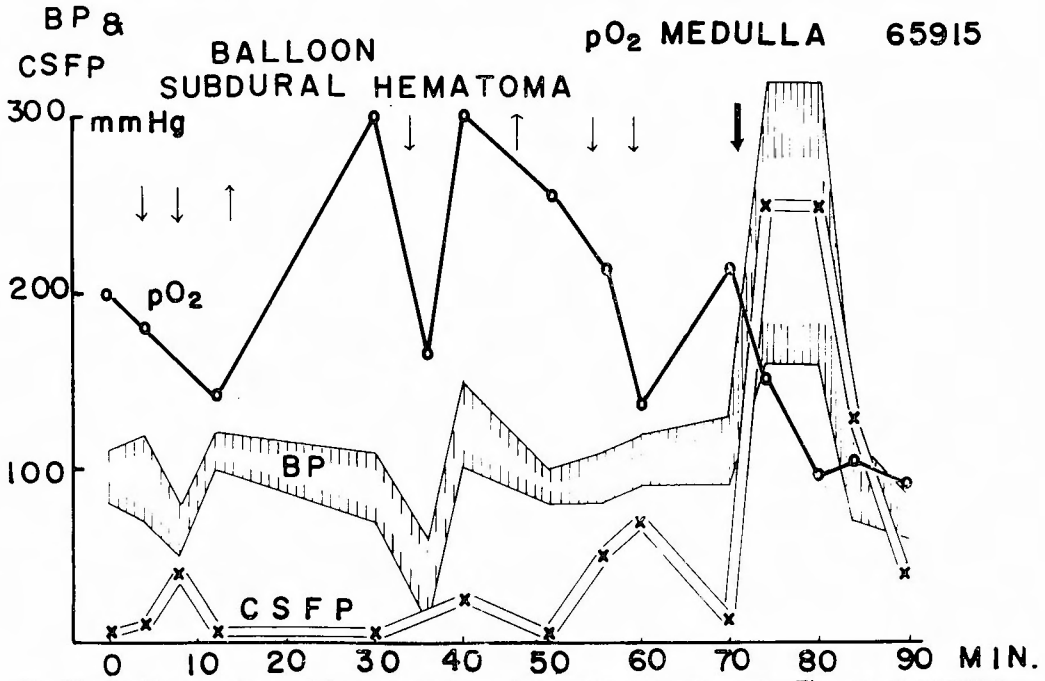

Fig. 13 : In this case, the two initial compression evoked vasodepressor responses. The vasopressor response was shown at the third compression with the pO_2 descent to 70%. Succeeding the arterial inflow, prominent increases both in cisternal pressure (250 mmHg = 3400 mmH_2O) and blood pressure were observed. The medullary pO_2 decreased to 48% accompanied by apnea. C. S. F. P. represents the cerebrospinal fluid pressure measured in cisterna magna. Arrows indicate compressions and decompressions. The last arrow indicates the arterial inflow.

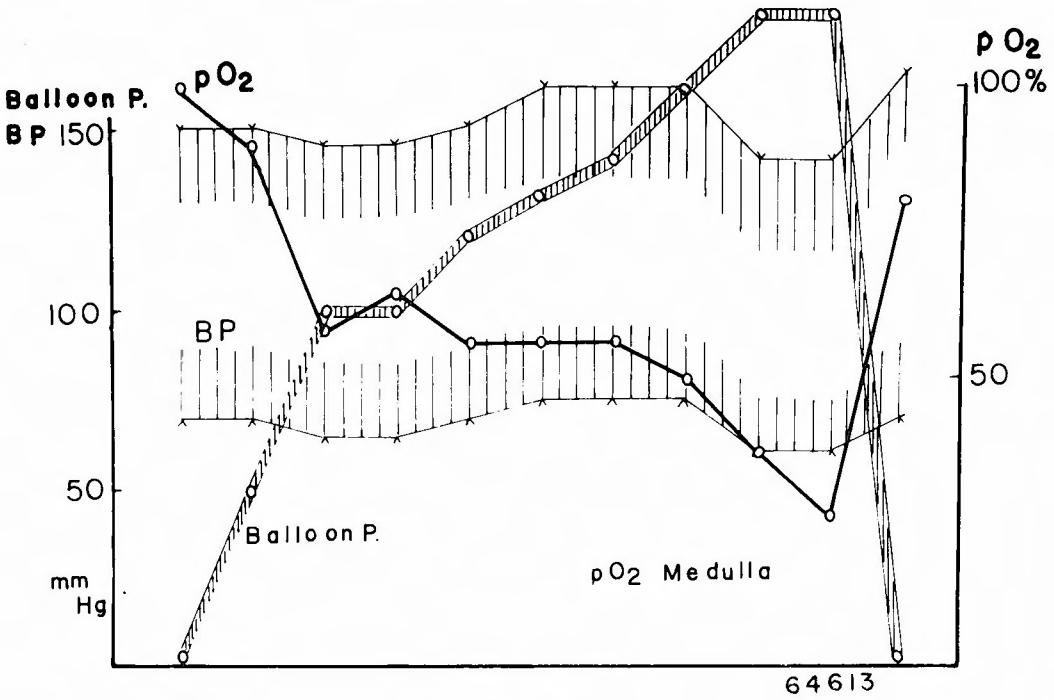

Fig. 14

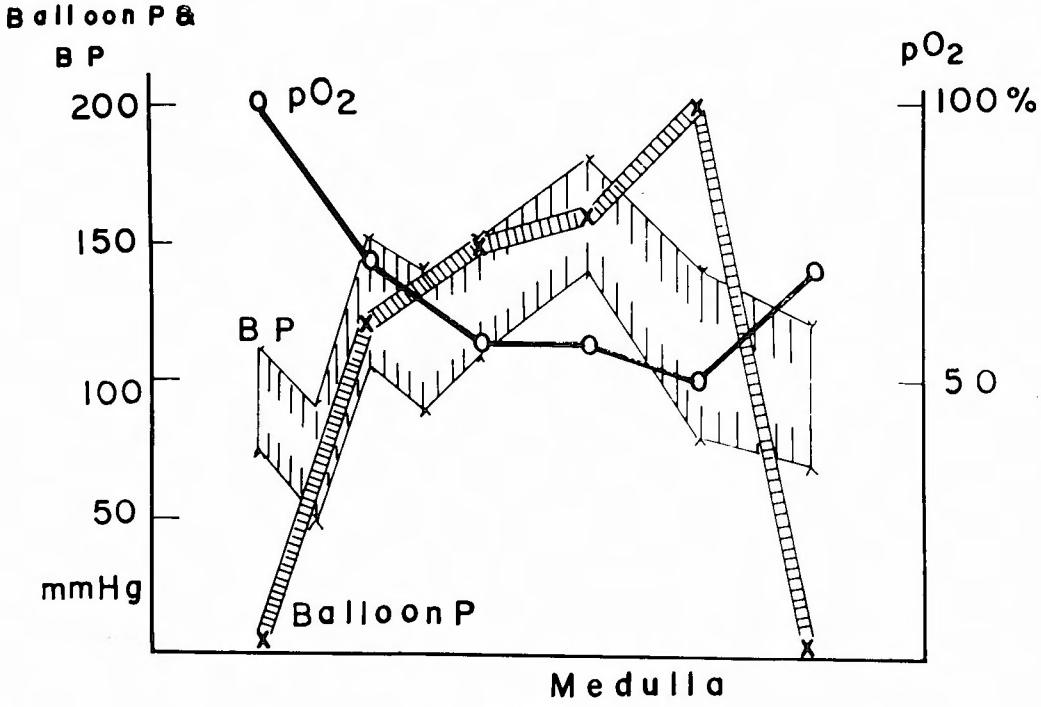

Fig. 15

Figs. 14 and **15** : Vasopressor responses and medullary pO_2. Marked decrease in medullary pO_2 was not observed until the compressing pressure exceeded the systolic blood pressure.

extreme anoxia lasting for 30 minutes. This indicated that the ischemic anoxia is not the sole cause of edema formation.

Following the initial phase of depression, the pO_2 tended to increase. However, this increase was soon interrupted by the progression of edema formation, as seen from pressure elevations, and the pO_2 began to decrease concomitant with the pressure increase and eventually reached zero after 14 hours. This compensatory mechanism of the cerebral circulation in intracranial hypertension was detected by pO_2 measurements only. It was demonstrated during the formation of intracranial hematomas as well as during compression.

Histological findings. In each animal both parietal cortices were sectioned in the frontal plane and blocks were removed from 1 cm lateral to the midline to include the cortical surface. As the cells were arranged more regularly in the white matter than in the cortex or cortico-subcortical border and so were more suitable for comparison, the cell densities in the white matter about 5 mm deep from the cortical surface were compared.

In cases of secondary elevation of intracranial pressure or of edema, the cell density was reduced to about 50% of the control and vacuolization was marked in both hemispheres.

In the case in which no elevation of pressure was observed in spite of compression, similar findings were observed on the compressed side but the cell density remained normal on the non-compressed side.

These findings suggest that a secondary elevation of intracranial pressure was produced when the local edema under the compressing balloon was propagated bilaterally throughout the brain.

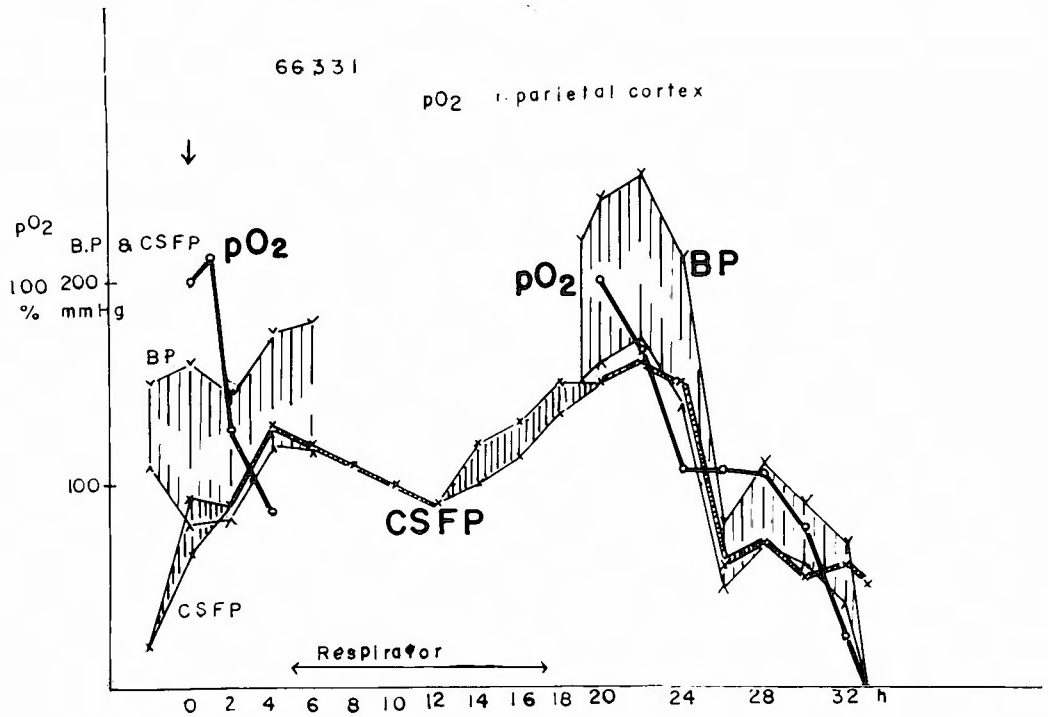

Fig. 16 The swelling after compression

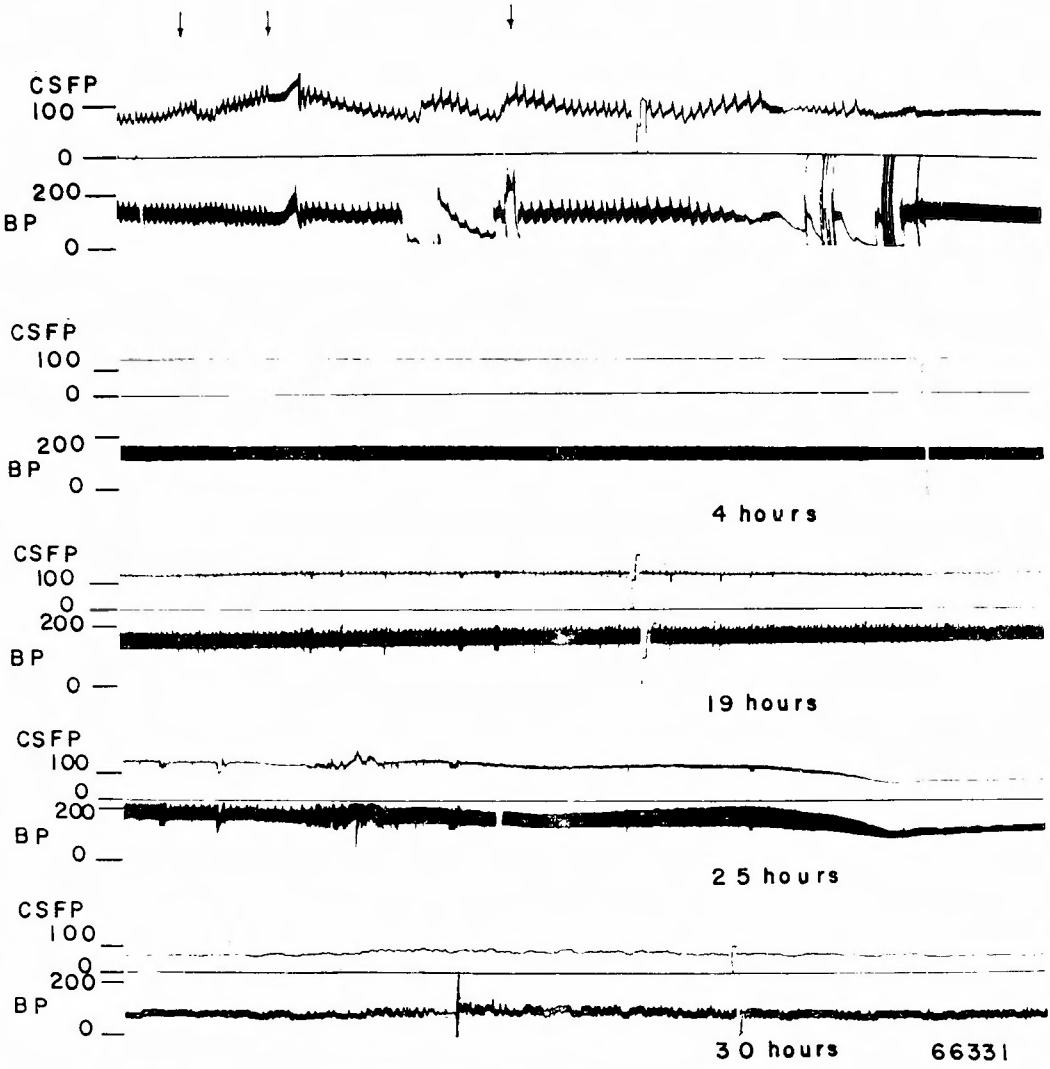

Fig. 17 The swelling after compression

Table 7

	Non-Compressed Hemisphere	Rate	Compressed Hemisphere	Rate
Normal Pressure (fig. 20)	538	100%	356	66%
Intracranial Hypertension (fig. 23)	288	54%	293	56%
Intracranial hypertension (fig. 16)	287	53%	226	42%
Intracranial Hypertension with Osmotic agents (fig. 18)	352	65%	335	62%

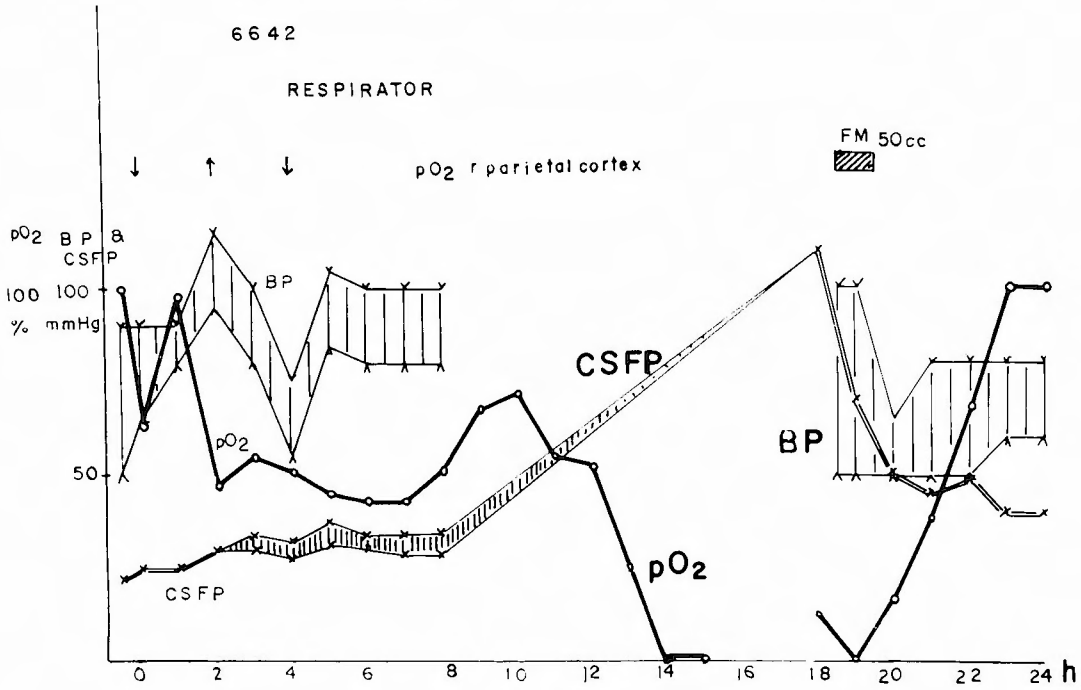

Fig. 18

Figs. 16, 17 and 18 : The development of the secondary elevation in intracranial pressure or swelling after compression was followed from 24 to 36 hours. Fig. 17 is the same case as Fig. 16. Compression was maintained throughout the experiment. The swelling progressed and the cerebrospinal fluid pressure reached a peak of 100 mmHg (1360 mmH_2O) 18 to 24 hours later. The pO_2 in the parietal cortex of the non-compressed hemisphere was reduced from 40 to 50% after compression and remained low for 3 to 5 hours. This prolonged hypoxia was considered responsible for the development of brain swelling. Arrows indicate the injections within the balloon.

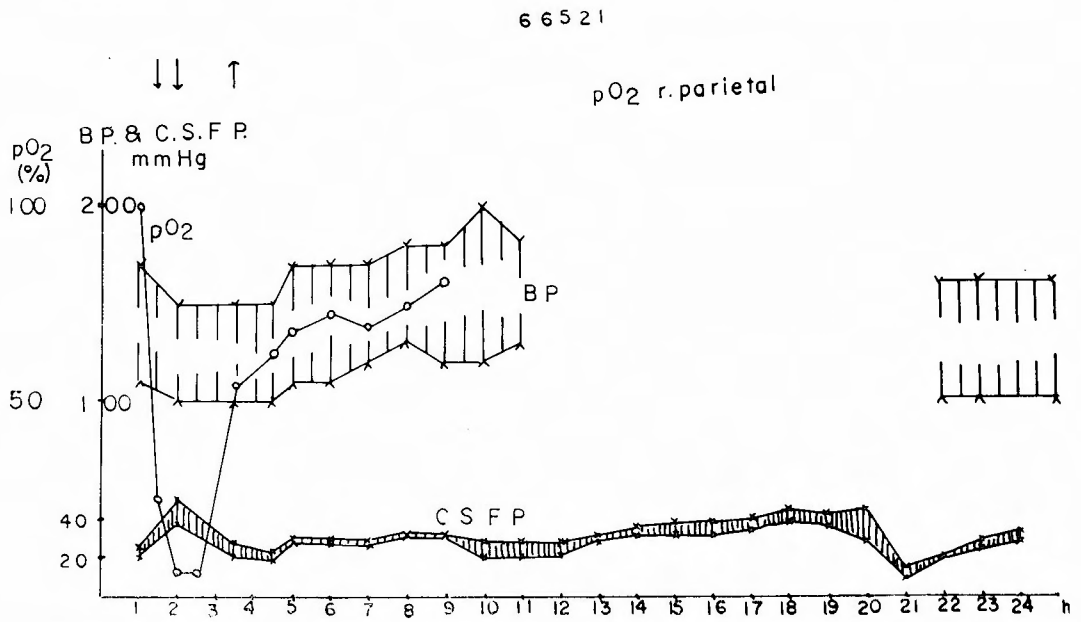

Fig. 19 : pO_2 was restored to 80% after 30 minutes of severe hypoxia. Partial removal of the compression produced no marked change in pO_2. In this case, a moderate increase in pressure (50 mmHg = 680mmH_2O) developed but showed no tendency to progress. The pressure decreased slightly after 24 hours.

In one case of edema treated with hypertonic agents, the cell density was only 10% more than in non-treated cases but far from normal although the intracranial pressure was reduced almost to normal.

The cell numbers in the same visual field (10×10) are compared in Table 7.

3) Intracranial hypertension througe saline injection.

Saline was injected into the cisterna magna. The cerebral oxygen tension decreased with increasing intracranial pressure, as illustrated in Figs. 21 and 22. A high pO_2 was maintained in the medulla also when intracranial hypertension was induced by this method. The pO_2 levels at the beginning of the pressor response are listed in Table 9.

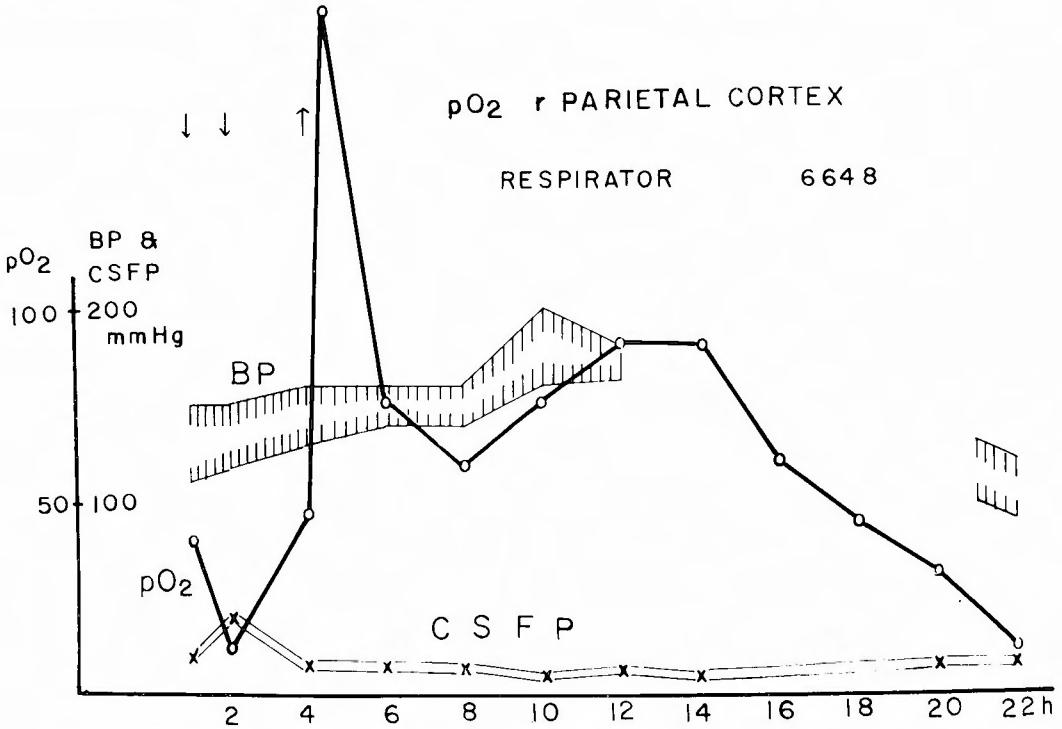

Fig. 20 · The compression was removed after 3 hours. The pO_2 rose above its original level after the decompression and remained high until 14 hours later. The cerebrospinal fluid pressure remained normal throughout the experiment. In this case, the anoxia was not severe nor prolonged, and decompression relieved the brain swelling.

4) Intracranial hypertension induced by arterial blood via catheter.

This procedure was employed to produce hydraulically a condition most closely resembling the intracranial hypertension of acute hematoma generally observed clinically.

A catheter 1 mm in o. d. carried the blood from one femoral artery into the closed intracranial space. Acute subdural hematoma was produced most often to improve and to ellucidate the poor clinical courses. The tip of the catheter was introduced subdurally through small incision in the dura mater. Extradural and intracerebral hematomas were also produced in a few cases.

With the start of inflow of arterial blood, rapid and severe increases in intracranial pressure were observed with marked decrease in tissue oxygen tension: these changes are

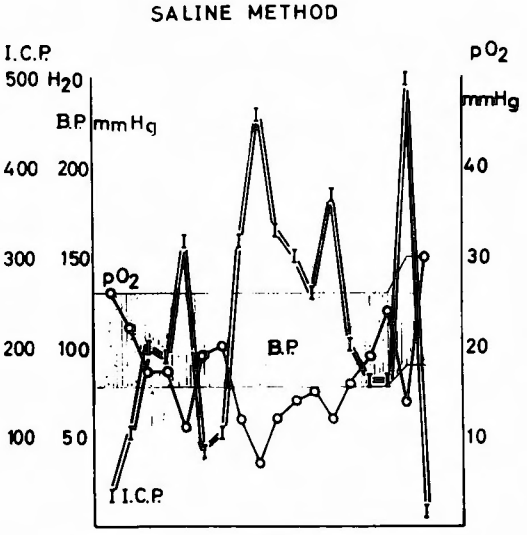

Fig. 21 : Saline injection into cisterna magna. Vasopressor response was observed when the cisterna magna. Vasopressor response was observed when the cisternal pressure reached 500 mmH_2O.

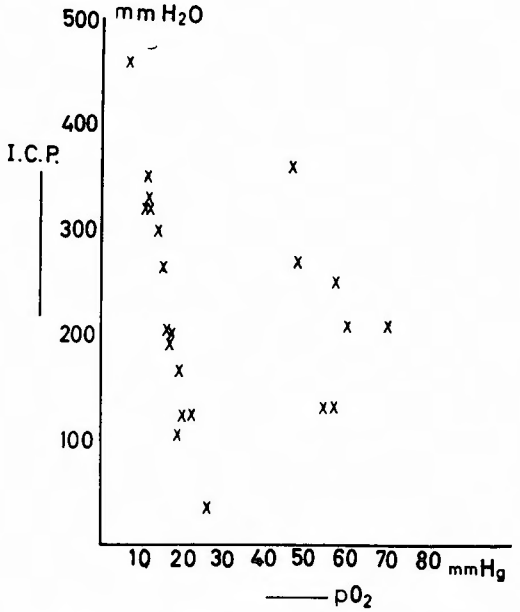

Fig. 22 : The relationship between cisternal pressure and pO_2.

Table 8 Vasopressor Response Balloon method

	Ball. p	CSFP	MBP	pO_2	
	120		87	72%	Medulla
	150		124	57	〃
	120		97	56	〃
	100		92	100	〃
	120		80	41	〃
	50		80	77	〃
	60		80	90	〃
	80		114	88	〃
	80		117	100	〃
		110	107	34	Mes
		120	87	7	〃
		53	103	30	Cortex
		22	85	55	Medulla
	220	10	177		
	200	9	143		
	300	20	182		
	60		117		
	220		122		
	270		100		
	210		143		
	190	30	103		
	250	60	103		
Mean	120	48	111		

Table 9 Vasopressor Response (Saline)

CSFP	MBP	pO_2	
37	97	54%	Dienc
18	70	71	Medulla
	107	96	Cortex
	108	18	〃
	110	0	〃
50	87	88	Medulla

Hematoma

	CSFP	MBP	pO_2	
	11	82	50%	Medulla
	70	125		
		143	41	venous
	230	117	62	Cortex
	250	103	41	Medulla
	72	63	15	venous
Mean	127	106		

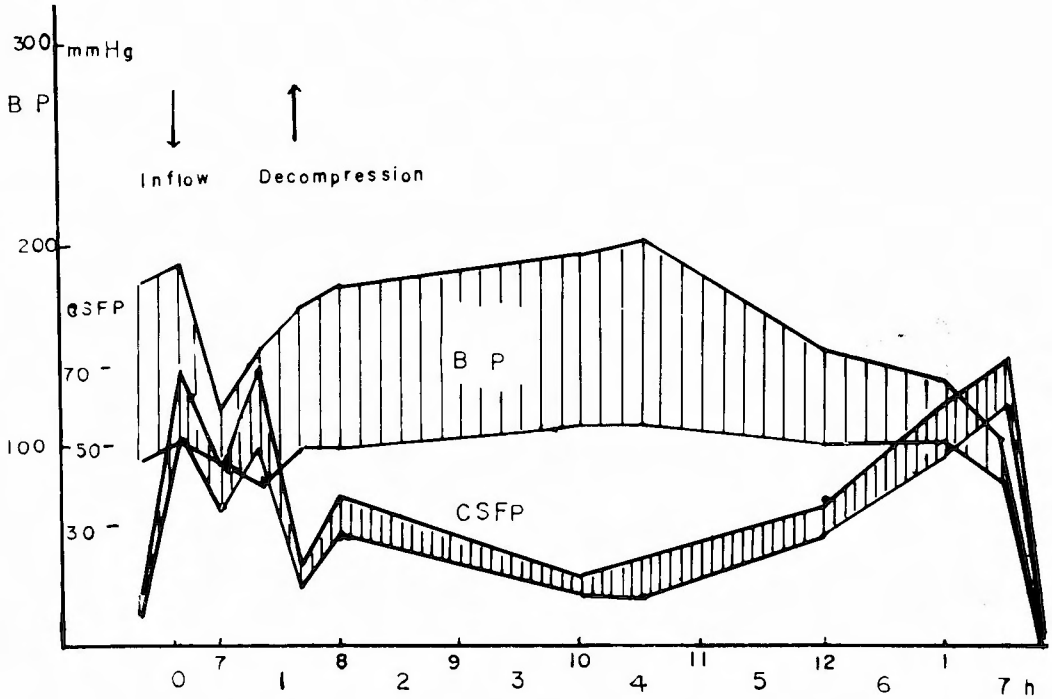

Fig. 23

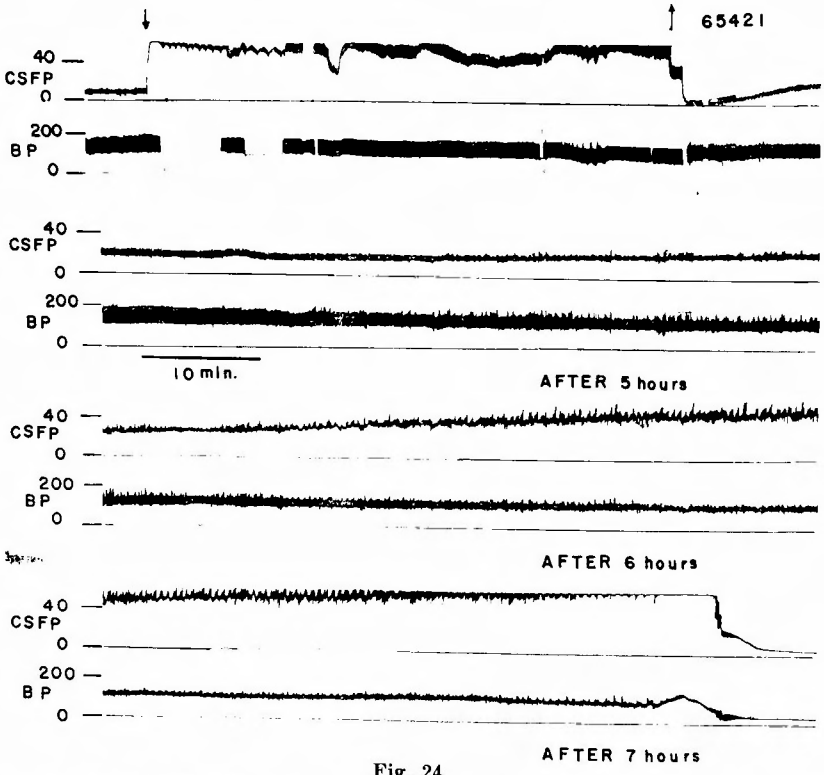

Fig. 24

Fig. 23 and 24 : Hematoma was produced and in this case removed after 40 minutes. The lowered cerebrospinal fluid pressure rose again and reached 70 mmHg (950 mmH_2O) after 7 hours.

considered to be due to the high arterial pressure and occlusion of the subarachnoid space with consequent restricted absorbtion of the cerebrospinal fluid. Usually 70 to 260 mmHg of intracranial hypertension were observed in experimentally produced intracranial hemorrhage as illustrated in Figs 23 through 30, and the venous oxygen tension was reduced to 15 to 40%, the oxygen tension of the cerebral cortex to 28%, and that of the medulla to 41% of the initial level; this was invariably followed by apnea. The severe intracranial hypertension remained for a short time and began to decrease gradually after 5 to 14 minutes. This gradual decrease in intracranial pressure can be explained as follows: as equilibrium is established between the pressure of the arterial inflow and the intracranial pressure, a hematoma develops due to interruption of the inflow and blood coagulation; then cerebral homeostasis results in a decrease in the vascular bed or elimination of superfluous cerebrospinal fluid from the intracranial space and leads to the descent of the intracranial pressure.

When adequate artificial respiration was maintained during the initial rise of pressure, the tissue pO_2 returned to above the critical level and the intracranial pressure began to decrease. The blood pressure also returned to normal, resulting in a stage of compensation.

Before the secondary rise of the intracranial pressure, some signs of compensation were observed in all surviving animals. A similar mechanism is considered to be present during the lucid interval observed clinically after head injury. Symptoms of intracranial hematoma have generally been blieved to progress as the hematoma develops. However, the present experiments suggest that clinical deterioration is more likely to be associated

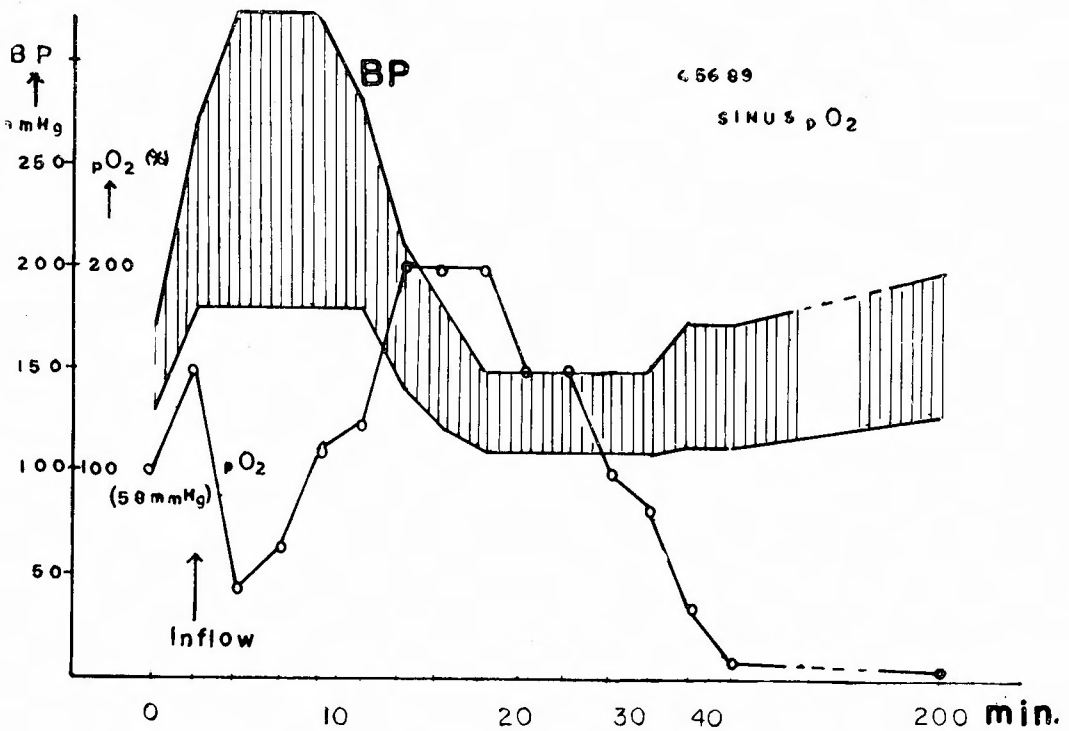

Fig. 25 Acute subdural hematoma

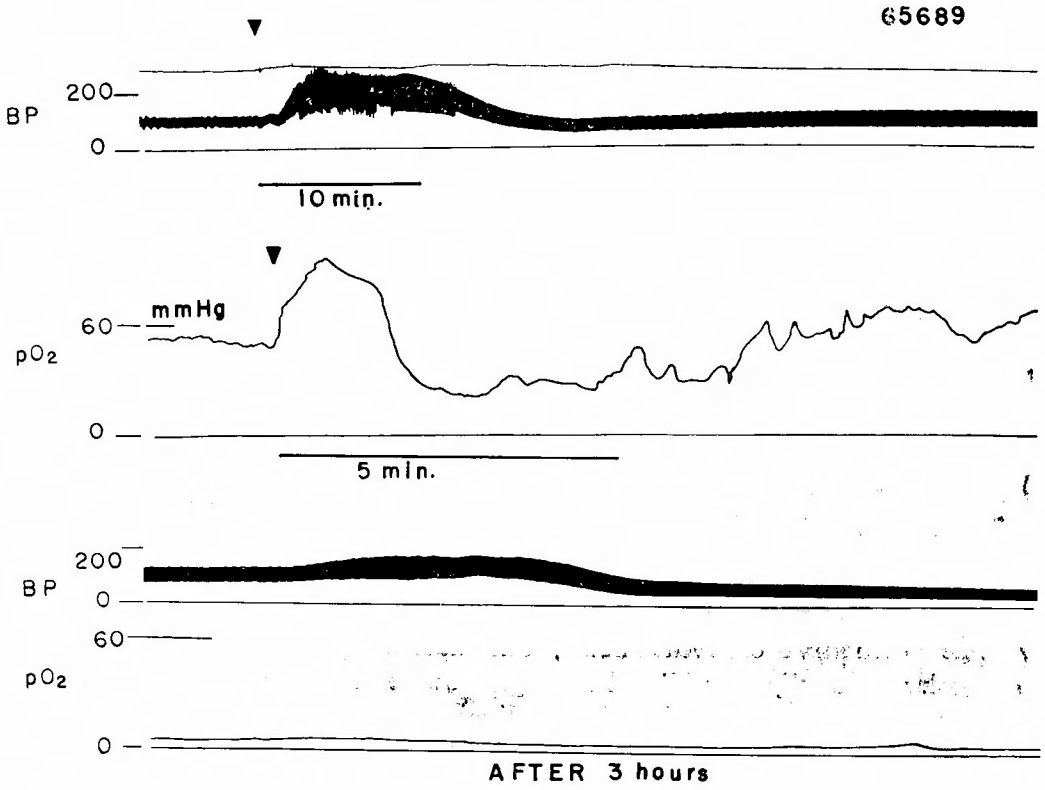

Fig. 26

Figs. 25 and 26 : Arterial blood was introduced subdurally. Succeeding the inflow, the pO_2 decreased in spite of the rise in blood pressure followed by compensatory pO_2 increase, and the vasopressor response returned to normal. Arrows indicate the arterial inflow.

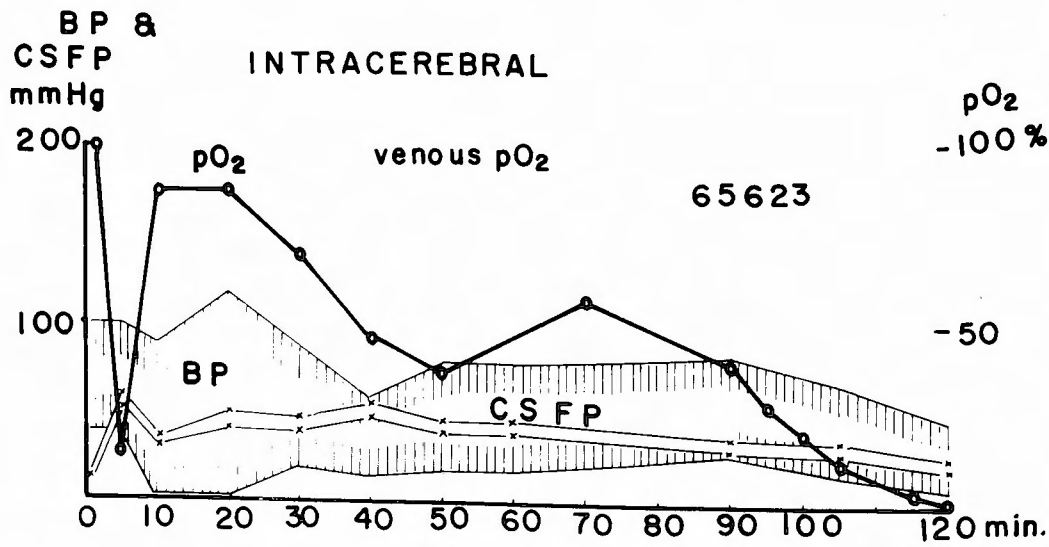

Fig. 27 Intracerebral hematoma

with the development of cerebral edema than with the formation of hematoma ; the latter may be formed relatively rapidly and be immediately followed by the stage of compensation. If treatment is inadequate during the stage of compensation, decompensation may be manifested before long, progressing eventually to cerebral edema and clinical deterioration. Early operation, consisting of removal of the expanding lesion or decompression is indicated during the stage of compensation.

5) Vasopressor response and variations of pO_2 in different areas of the brain.

The above experiments showed that as the intracranial pressure increases the pO_2 of the cerebral tissue decreases. If no acute rise in metabolism occurs, the observed pO_2 decrease obviously reflects a decrease of local blood flow, that is, the anoxia is ischemic anoxia. A vasopressor response did not occur until the cisternal pressure reached a mean of 48 mmHg by the balloon method or of 35 mmHg by the saline method. Around these intracranial pressures, the pO_2 of the cerebral cortex, mesencephalon, diencephalon and

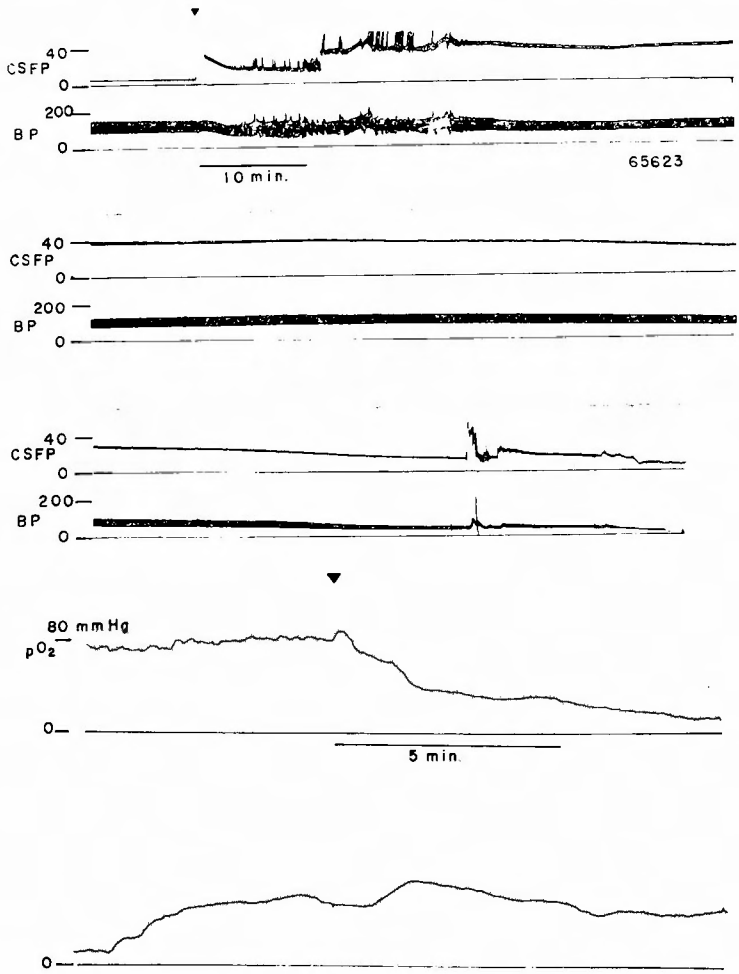

Fig. 28

Figs. 27 and 28 : Intracerebral hematoma produced by arterial blood.

cerebral venous blood were markedly reduced to below the critical level and danger of irreversible tissue damage was imminent. In contrast, the medulla oblongata was protected from these insults, and the pO_2 remained above the critical level in the majority of cases (Table 6). Experimental animals survived when the pO_2 of the medulla remained above the critical level even when the pO_2 of other areas was markedly reduced.

6) Vasopressor response in relation to intracranial pressure and mean blood pressure.

Vasopressor response, i. e., elevation of blood pressure, has been considered to occur when the intracranial pressure equals the mean systemic blood pressure. The authors experiments indicate that this is not necessarily true, and vasopressor responses were observed even at lower intracranial pressures. As shown in Tables 8 and 9, this phenomenon was observed at a mean balloon pressure of 120 mmHg, a mean cisternal pressure of 48 mmHg and a mean systemic blood pressure of 110 mmHg with the balloon method, and at a mean cisternal pressure of 35 mmHg and a mean systemic blood pressure of 96.5 mmHg with the saline method.

However, the high mean balloon pressure indicates that high local pressure, even when the cisternal pressure is low, is effective in evoking the response. Pressure differences between the supratentorial and infratentorial compartments may be related to this response. When the intracranial pressure was made to exceed the systolic blood pressure, the animal immediately developed hemodynamic decompensation, and the blood pressure began to decrease progressively accompanied by a sharp decrease of pO_2 until the animal died.

The rise of blood pressure widely observed in patients with intracranial hemorrhage may be the manifestation of vasopressor response caused by increased intracranial pressure.

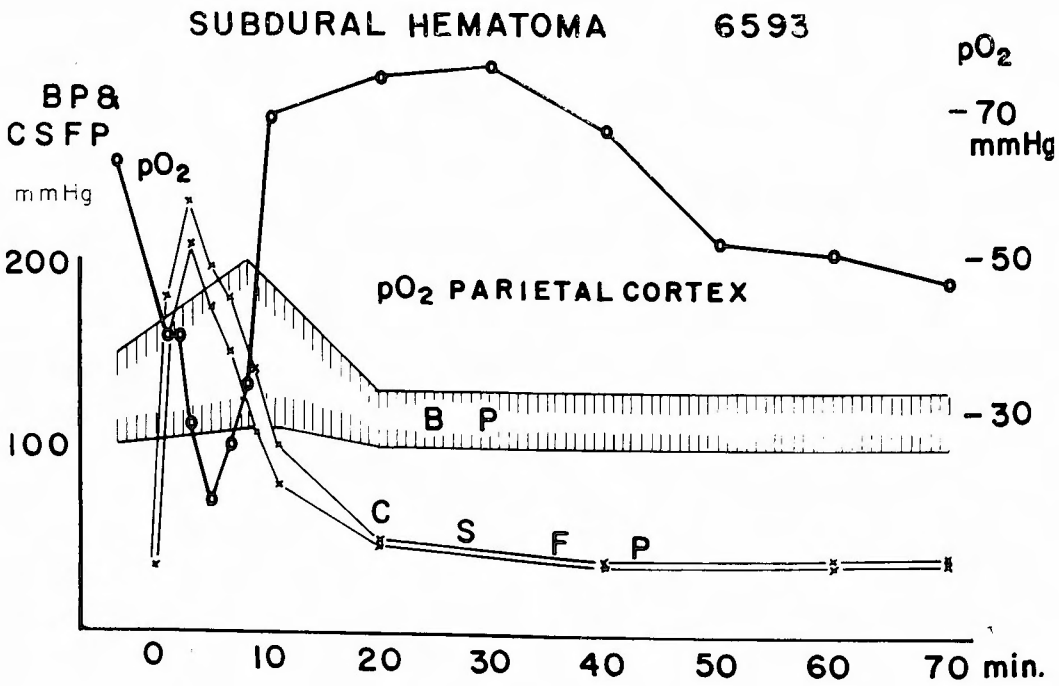

Fig. 29 Subdural hematoma

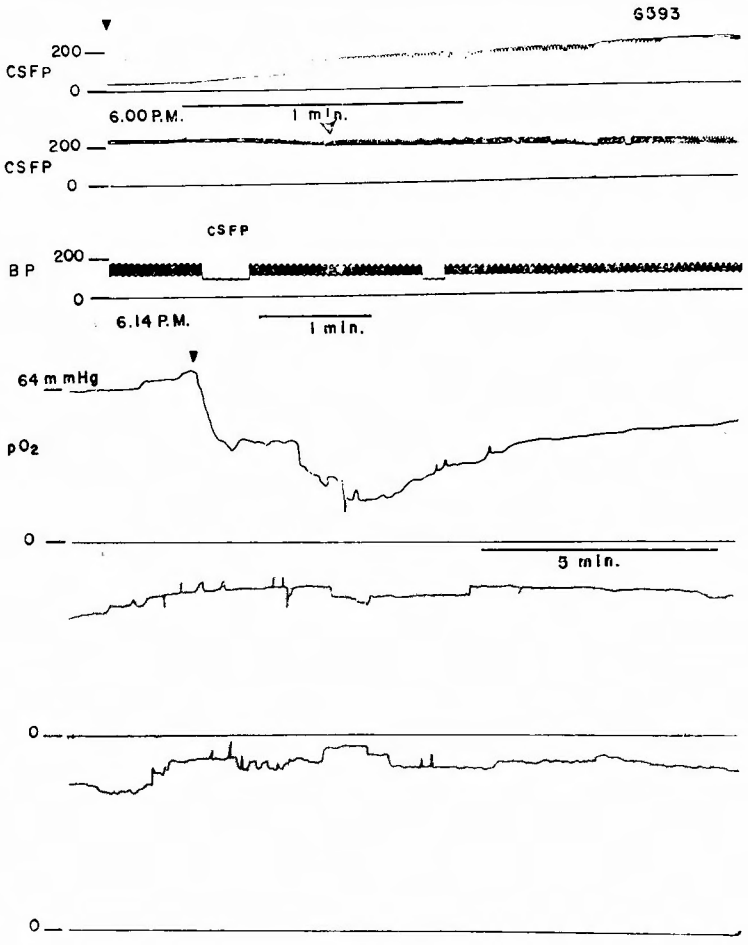

Fig. 30

Figs. 29 and 30 : Subdural hematoma.

3. DISCUSSION

1) Methods of producing ischemic anoxia.

The brain of the dog is much better supplied with vascular anastomoses than that of man. Moreover, there are anastomoses between the internal and external carotid arteries, and between the extracranial and intracranial arteries ; the collaterals in the neck include intramuscular vessels, the A. mammalia interna, A. spinalis, A. occipitalis,. As all of these carry blood to the brain, induced ischemic anoxia may be interfered with and the results obtained may vary greatly if the procedures employed are inadequate. Therefore, the author used mainly systemic hypotension and intracranial hypertension to produce ischemic anoxia, thus avoiding interference by collateral circulation.

2) Relation of tissue pO_2 to local blood flow and relation of venous pO_2 to total blood flow in the brain.

According to Meyer, Denny-Brown and other investigators in this field, tissue pO_2

is determined by three factors: 1) arterial pO_2, 2) local blood flow, 3) local oxygen consumption.

Tissue pO_2 may increase or decrease depending upon the change of these three factors. If pO_2 decreases, the conceivable causes are 1) decrease of arterial pO_2 2) decrease of local blood flow 3) increase in local oxygen consumption.

While the increase in oxygen consumption cannot be considered to occur in ischemic anoxia, the main cause of the decrease in tissue pO_2 is the decrease in local blood flow in a range in which the arterial pO_2 does not decrease.

Hence, tissue pO_2 was used as an indicator of local blood flow or of ischemia.

The relation among oxygen consumption, blood flow and oxygen content of the blood is expressed as follows:

$$CMRO2 = F \times (aO_2 - vO_2)$$

where $CMRO_2$: oxygen consumption
F : blood flow
aO_2 : oxygen content of the arterial blood
vO_2 : oxygen content of the venous blood

In situations in which arterial oxygen content and tissue oxygen consumption do not change, blood flow can be expressed as a function of venous oxygen content. If HILL's equation concerning the oxygen dissociation curve is brought into above fomula, the blood flow can be calculated as a function of venous oxygen tension.

HILL's equation : $$\frac{y}{100} = \frac{kx^{2.5}}{1 + kx^{2.5}}$$

y : O_2 saturation of hemoglobin
x : oxygen tension
k : dissociation constant

As was shown in a preliminary experiment, the oxygen tension of the cerebrospinal fluid parallels the total blood flow of the brain. However, more detailed investigation is needed to establish the relationship quantitatively.

3) Tissue pO_2 and blood pO_2 after oxygen inhalation.

TSAO et al[18] reported a 4 fold increase in the pO_2 of arterial blood during inhalation of 80% oxygen. Other reports and also the experiments of the author confirm this.

The report[10] that posthypoxic hyperoxia is greater than simple hyperoxia was also confirmed. As to the decrease of cortical pO_2 during hyperventilation[1)23)] reported by some authors, experimental results are lacking in this study.

MEYER et al[19] state that cortical pO_2 decreases after the inhalation of 100% oxygen due to a concomitant fall in blood pressure. In this experiment no such finding was observed.

4) Anesthesia.

As was shown in the above experiments, the tissue pO_2 of the brain was decreased during ether anesthesia. However, Meyer et al found that the EEG is a more sensitive indicator of the depth of anesthesia than the cortical oxygen polarogram.

LASSEN states that brain metabolism decreases to 40-50% during surgical anesthesia but that the cerebral blood flow is not so markedly reduced. However, if such a situation exists, the tissue pO_2 should increase during anesthesia and it does not. In conclusion,

it is pertinent to state that the cortical pO_2 is not a good index of the depth of anesthesia.

5) Oxygen tension of cerebrospinal fluid measured in the cisterna magna.

JARUM et al[12] observed in man the shifts of oxygen tension of cerebrospinal fluid following the rise and fall of blood pressure and found that the oxygen tension rose during O_2 inhalation from an original level of 40 mmHg to 70 mmHg less than did arterial oxygen tension. He considered that the cisternally measured oxygen tension of the cerebrospinal fluid represented the mean oxygen tension of the surrounding cerebral tissue and it was an acceptable way of estimating rapid changes in cerebral blood flow.

6) Hypotension.

WEINSTEIN et al[25] stated that the blood flow in the neck decreased linearly with the fall of blood pressure during blood withdrawal of up to one hour. SCHNEIDER[21][24] stated that cerebral blood flow and systemic blood pressure changed linearly during rapidly induced hypotension but that during slowly induced hypotension the blood flow decreased only slightly, due to compensatory vasodilation, until a critical blood pressure was reached, below which the flow declined rapidly.

According to LASSEN[17] consciousness was disturbed and the EEG became abnormal when the cerebral venous oxygen tension reached 15 to 20 mmHg. During slowly induced hypotension, the change of blood flow was not remarkable in the blood pressure range of 180 to 60 mmHg. Below 60 mmHg the flow change was marked. When the blood pressure fell to 40 to 50% of the control value, the flow decreased to 60% and was in critical level, but the fall of oxygen consumption was not remarkable.

The studies of HIRSH and associates[9] indicate that the cerebral oxygen consumption of 3.90 ml/100g/min. at cerebral venous oxygen tensions of above 20 mmHg began to decrease below venous oxygen tensions of 17 to 19 mmHg and was reduced to 1.6 ml/100g/min. (41%) at 11 to 12 mmHg, but the EEG remained active even then.

SAGAWA[22] and associates discovered by cerebral perfusion experiments that the vasopressor response became intense due to cerebral ischemia at cerebral perfusion pressures of less than 40 mmHg or at cerebral blood flows of less than 2.0 ml/100g/min. (51%).

In experiments where hypotension was rapidly induced until the required blood pressure was obtained, no vasopressor response to cerebral ischemia appeared and rapid decompensation progressed after functional disturbance of the vasomotor center occurred. (The function of the vasomotor center has been considered to be depressed after 5 to 6 minutes of blood pressure around 40 mmHg). This compensatory vasopressor response was thoroughly studied in this experiment on ischemia during intracranial hypertension.

The oxygen consumption during hypoxia was also investigated biochemically. According to CHANCE[5] oxidase activity depends upon a supply of substrate and is not influenced by the amount of oxygen above the critical oxygen tension, below which the oxidation of oxidase comes to depend upon the concentration of oxygen, and the rate of oxidation decreases rapidly under such conditions. The studies of THEWS[24] showed that cytochrome oxidase activity was reduced to 83% at tissue oxygen tensions under 4 mmHg. DAVIES and BRONK[7] observed the oxygen tension of the pial veins to fall from 25 mmHg to 0 mmHg after compression. They said that the oxygen activating system began to be unsaturated at tissue oxygen tensions below 5 mmHg. In summary it may be stated that though the decrease of cerebral blood flow is linear during rapidly induced hypotension,

it is not linear and shows a critical level during slowly induced hypotension. Oxygen consumption is said to decrease at venous oxygen tensions below 19 mmHg or at tissue oxygen tensions below 4 to 5 mmHg.

In my experiments where blood was withdrawn rapidly in less than two hours, the cortical oxygen tension demonstrated a critical level during the progress of hypotension. This non-linearity is considered to indicate that the compensation is effective above a critical level and not effective below. Not only the homeostasis to increase blood flow after ischemia such as vasodilation, the vasopressor response and carotid reflexes, but also the metabolism of compensation, namely the decrease in cerebral metabolism to compensate for reduced blood supply, should be considered in the above measurements. During acute ischemia some degree of decrease in oxygen consumption may play a part in homeostasis to prevent irreversible tissue damage, and the rapid fall of pO_2 below the critical level of pO_2 is considered to indicate that even the decrease in oxygen consumption does not work compensatorily below this level.

Although the cerebral metabolism has been considered to decrease at venous oxygen tensions below 19 mmHg or at tissue oxygen tensions below 5 mmHg, what is important is not the reduction of metabolism but the state in which the tissue can no longer be reserved intact in spite of the reduction of metabolism, namely the state in which irreversible tissue damage is manifested through metabolic decompensation. Not only the degree of ischemia, but also the duration, should be considered in a discussion of irreversible tissue damage. In my studies half the experimental animals died after 8 to 13 minutes of ischemic anoxia in the medulla at tissue oxygen tensions below 70%, or the critical level. The duration and degree of ischemic anoxia needed to cause irreversible tissue damage await further investigation.

7) Intracranial hypertension.

WEINSTEIN et al[15)16)25)] considered the progress of intracranial hypertension as the progress of cerebrovascular decompensation and divided it in 4 stages. In the first stage of intracranial hypertension vasomotor paralysis mainly due to ischemic anoxia and accumulation of carbon dioxide produces vasodilatation and an increase in intracranial blood volume. In the second stage, the intracranial pressure approaches the vasopressor threshold, and both arterial and intracranial pressure are elevated. In the third stage, the intracranial pressure approaches the arterial pressure resulting in severe cerebral ischemia, and vascular decompensation begins. The arterial pressure begins to decrease, and progressive brain swelling ensues. In the fourth stage, the vascular decompensation becomes irreversible, and the cerebral blood flow ceases entirely. He states that the vasomotor paralysis is the essential feature through all stages. In their study, the intracranial pressure and cervical blood flow exhibit an inverse linear relationship during the the process of increasing intracranial pressure. These results coincide well with my experiments, in which the same inverse linearity was found between the intracranial pressure and cerebral oxygen tension.

On the other hand, KETY and SCHMIDT[13)] studied the cerebral blood flow, using the N_2O method on patients with intracranial hypertension consisting mainly of brain tumors and reported that the decrease in flow did not occur until the intracranial pressure reached 450 mmH_2O (33 mmHg).

These opposite tendencies are considered to indicate that the blood flow of the brain

tends to decrease during acutely induced intracranial hypertension while it is not so easily decreased in chonic intracranial hypertension due probably to an as yet unrecognized compensatory mechanism to maintain effective blood flow to the brain.

In the measurement of blood flow, reports on the observation of microcirculation should not be disregarded (FAZEKAS, PAPPENHEIMER). The normal capillary pressure in man is estimated to be around 24 mmHg. When the tissue pressure is elevated, the capillaries are occluded and the areas distributed become ischemic even though the blood flows through arteriolo-venous anastomoses or collateral channels.

Under these situations, the macroscopic flow measurements as determined by the N_2O method or electromagnetic flowmeter do not indicate the reduction of flow until even these anastomoses are occluded. At present, the measurement of oxygen tension is the most valuable method estimating the effective blood flow or the true capillary flow.

8) Vasopressor response.

The vasopressor response was defined by WEINSTEIN[25] as the elevation of systolic or diastolic blood pressure or both above the control level by increasing the intracranial pressure. They stated that the primary center of the vasopressor response is probably situated supratentorially and the response is evoked by local ischemia or local pressure. The response is more easily evoked by an intracerebral expanding lesion than by an extracerebral expanding lesion. The secondary center is situated caudal to the superior border of the inferior olive and able to produce the response by itself after the primary center is destroyed.

The threshold of the secondary center is around the mean blood pressure. The threshold for the response is lower when there is a pressure gradient between the supra- and infratentorial compartments. Variable thresholds could be demonstrated with uniform increase of intracranial pressure.

These centers demonstrate a lower threshold after repeated experiments but lose their reactivity after a certain degree of damage. These experimental results and conclusions of WEINSTEIN et al agree with my results, and their hypothesis was in part proved. Namely, local ischemic anoxia was demonstrated supratentorially but not in the medulla oblongata concomitant with the vasopressor response.

When the intracranial pressure is elevated around or above systolic blood pressure, the blood flow through the brain ceases entirely causing respiratory and cardiac arrest within a few minutes. Even with lower intracranial pressure where the oxygen tension is reduced below the critical level and the vasopressor response begins to be manifest, the tissue damage is beginning to be irreversible. The mechanism of the maintenance and decompensation of homeostasis during ischemic anoxia is one of the most important subjects in both the study and treatment of neurological disorders and awaits thorough investigation.

4. SUMMARY AND CONCLUSIONS

Since there have been only a few methods of measuring local blood flow of the brain, the author observed the changes of tissue oxygen tension polarographically at various areas within the brain during ischemic anoxia of the brain, particularly under systemic hypotension and intracranial hypertension.

The principle and the significance of this method was also discussed. From the experiments the following conclusions were deduced.

1) The oxygen tension of the cisternal cerebrospinal fluid was in almost linear relation with the systemic blood pressure and reacted within one minute after the change of the blood pressure. It probably reflects the total blood flow of the brain.

2) The blood flow of the brain of the dog is almost completely compensated during occlusion of the cervical arteries by collateral circulation. The latter fails at comparatively higher blood pressures around 90 mmHg systolic.

3) While the blood does not flow through the circle of WILLIS in normal brains, about 15% of the cortical oxygen supplied by middle cerebral artery was estimated to flow with blood through the circle of WILLIS when unilateral common carotid occlusion was performed and 65% of oxygen was transported through the circle of WILLIS when bilateral common carotid ligation was performed, indicating the significance of the circle of WILLIS in vascular disorders.

The remaining oxygen supplied to the cortex was 35% immediately after occlusion and increased later to 81% due probably to opening of collateral circulation or local vasodilatation.

4) During controlled systemic hypotenion, the oxygen tension of cerebral tissue fell rapidly at systolic blood pressures of 55 to 70 mmHg. This is the critical level of blood pressure. Half the animals exposed to anoxia for 8 to 13 minutes at oxygen tensions below 70% of the original value died in spite of blood transfusions. In the remaining half, the oxygen tension was restored following the recovery of blood pressure.

5) The rate of decrease of tissue oxygen was greater during hexamethonium-induced hypotension than during hemorrhagic hypotension indicating the greater danger of neurogenic than of hemorrhagic shock.

6) During the ischemic anoxia induced by intracranial hypertension, the changes of oxygen tension were different among various parts of the brain. Far lower degrees of anoxia were observed in the medulla oblongata than the anterior parts of the brain.

The elevation of blood pressure in CUSHING-phenomenon is considered to be not related to medullary ischemia, but triggered by ischemia of the superior brain.

7) Prolonged severe ischemic anoxia was observed in the first stage in experimental edema formation after the compression by balloon. Then the oxygen tension was restored to above 50% in the second stage followed by gradual decrease with the development of secondary intracranial hypertension or brain swelling.

8) Decreased cell density was observed bilaterally in cases with secondary elevation of intracranial pressure or edema while only unilateral decrease in cell density on the compressed side was observed in cases without elevation of the pressure.

9) In experimental intracranial hematoma, primary elevation of intracranial pressure was caused by hematoma. The pressure then decreased owing to autoregulation of the brain followed by secondary elevation of pressure through propagated cerebral swelling. During the compensatory stage, the oxygen tension of the tissue was restored above the critical level. Early operation is needed before secondary elevation of the intracranial pressure progresses.

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REFERENCES

1) Adams, John E. and Severinghaus, Jahn W. Oxygen tension of human gray and white matter. The effect of forced hyper-ventilation. J. Neurosurg. **19** : 059-970, 1962.
2) Bedford, T. H. : The effect of variations in the subarachnoid pressuse on the venous pressure in the superior longitudinal sinus and in the torcular of the dog. J. Physiol. **101** : 362-368, 1942.
3) Bloor, B. M., Fricher, J., Hellinger, F., Nishioka, K. and McGutchen, J. A study of cerebrospinal fluid oxygen tension. Arch. Neurol. **4** : 37-46, 1961.
4) Bradford, F.K. and Sharkey, P. C. Physiologic effects from the introduction of blood and other substances into the subarachnoid space of dogs. J. Neurosurg. **19** : 1017-1022, 1962.
5) Chance, Britton. : Cellular oxygen requirements. Fed. Proc. **16** : 671-680, 1957.
6) Davies, P. W. and Brink, F. Jr. : Direct measurement of brain oxygen concentrations with a platinum electrode. Fed. Proc. **1** : 19, 1942.
7) Davies, P. W. and Bronk, D. W. : Oxygen tension in mammalian brain. Fed. Proc. **16** : 689-692, 1957.
8) Hedges, T. R. and Weinstein, James, D. : Cerebrovascular responses to increased intracranial pressure. J. Neurosurg. **21** : 292-297, 1964
9) Hirsch, H., Gleichmann, V., Kristen, H., und Magazinovic, V. : Uber die Beziehung zwischen O_2-Aufnahme des Gehirns und O_2 Druck im Sinusblut des Gehirns bei uneingeschränkter und eingeschränkter Durchblutung. Pflügers Arch. **273** : 213-222, 1961.
10) Ingvar, David H., Lubbers, Dietrich W. and Bosiesjo : Measurement of oxygen tension on the surface of the cerebral cortex of the cat during hyperoxia and hypoxia. Acta physiol scand. **48** : 373-381, 1960.
11) Ishikawa, Susumu : Polarographic studies on cerebral collateral circulation, with special references to their clinical applications. Archiv für Japanische Chirurgie. **30** : 303-328, 1961.
12) Jarnum, S., Lorenzen, I. and Skinhoej, E. : Cisternal fluid oxygen tension in man. Neurology **14** : 703-707, 1964.
13) Kety, S. S., Shenkin, H. A. and Schmidt, C. F. : The effect of increased intracranial pressure on cerebral circulatory functians in man. J. clin. invest. **27** : 493-499, 1948.
14) Krogh, August : The number and distribution of capillaries in muscles with calculations of the oxygen pressure head neccessary for supplying the tissue. J. physiol. **52** : 409-415, 1919.
15) Langfitt, Thomas W., Weinstein, James D. and Kassel, Neal F. : Cerebral vasomotor paralysis produced by intracranial hypertension. Neurology **15** : 622-641, 1965.
16) Langfitt, Thomas W., Kassel, Neal F. and Weinstein, James D. Cerebral blood flow with intracranial hypertension. Neurology **15** : 761-773, 1965.
17) Lassen, N. : Cerebral blood flow and oxygen consumption in man. Physiol. rev. **39** : 183-238, 1959.
18) Makepeace, V., Vsao and Vadnay, Atilla : An electrode for continuous measusement of transient blood pO_2 in the vessel. J. appl. physiol. **15** : 712-716, 1960.
19) Meyer, J. S., Fang, H. C. and Denny-Brown, D. : Polarographic study of cerebral circulation. Arch. neurol. psychiat. **72** : 296-312, 1954.
20) Neely, W. A. and Youmans, J. R. : Anoxia of canine brain without damage. J.A.M.A. **183** : 1085-1087, 1963.
21) Opitz, E. und Schneider, M. : Uber die Sauerstoffversorgung des Gehirns und den Mechanismus von Mangelwirkungen. Ergebnisse d. Physiol. **46** : 126-260, 1950.
22) Sagawa, Kiichi, Ross, Joe M. and Guyton, Arthur, G. : Quantitation of cerebral ischemic pressure in dogs. Amer, J. physlol. **200** : 1161, 1961.
23) Sugioka, K. and Davis, D. A. : Hyperventilation with oxygen : a possible cause of cerebral hypoxia. Anesthesiology **21** : 135-148, 1960.
24) Thew, G. : Implication to physiology and pathology of oxygen diffusion at the capillary level : in "Selective Vulnerability of the Brain in Hypoxaemia" by Shade, J. P. and McMenemey, W. H., F. A. Davis Co. Philadelphia, 1963.
25) Weinstein, James D., Langfitt, Thomas W. and Kassel, Neal F. Vasopressor response to increased intracranial pressure. Neurology **14** : 1118-1131, 1964.
26) Wolff, H. G. and Forbes, H. S. : The cesebral circulation V. Observations of the pial circulation during changes in intracranial pressure. Arch. neurol. psychiat. **20** : 1035-1047, 1928.

和文抄録

人為的低血圧及び頭蓋内圧亢進時に於ける大脳組織酸素分圧の実験的研究

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虚血性アノキシアは，中枢神経系の病態生理学に於いて最も重要な問題の一つである．脳局所血流量を知る方法が未だ確立されていない所から，著者はポーラログラフの原理に基き，脳虚血時，殊に低血圧及び頭蓋内圧亢進の際の脳虚血性アノキシアにおいて脳組織酸素分圧を脳内各所に於いて測定した．測定原理についても考察を加え，実験からは次の結論が得られた．

1) 大槽内に於いて測定した脳脊髄液酸素分圧は血圧と殆んど直線的な関係にあり，一分以内に血圧変動を反映する．この酸素分圧は，恐らく全脳流血量を反映するものと推定される．

2) 犬の脳血流は，頸部血管閉塞時，血圧上昇と，副側血行に依つてほぼ完全に代償されるが，代償的副側血行は，收縮期血圧90以下では働かなくなる．

3) 正常では血流は Willis 輪を通らないか，一側総頸動脈を閉塞すると，中大脳動脈より脳皮質に至る酸素の15%は Willis 輪を通る様になり，両側総頸動脈閉塞では65%が Willis 輪を通る様になつて，血管障害時に於ける Willis 輪の重要性が確かめられた．

4) 人為的全身低血圧の際，脳組織酸素分圧は，全身血圧が55～70mmHg になつた時急速に低下し，Critical level を示した．この Critical level 以下に 8～13 分置いた犬の約半数は輸血にも拘らず死亡し，残りの半数は血圧と共に酸素分圧も回復した．

5) 脳組織酸素分圧の減少は Hexamethonium 注射に依る低血圧の際の方が，脱血に依る低血圧の際よりも急激であり，神経性ショックの方が出血性ショックよりも危険である事を示した．

6) 頭蓋内圧亢進の際，脳組織酸素分圧は脳内の場所によつて異り，延髄では酸素分圧が最も高く保たれた．Cushing 現象の際の血圧上昇は延髄虚血に依るものではなく，より上位の脳より惹起されるものであると思われる．

7) バルーンに依る実験的脳浮腫作製の際，圧迫により，第一期には遷延した極度のアノキシアがみられる．次いで第二期に，脳組織酸素分圧は元の50%以上に回復したが，二次性の脳圧上昇と共に再び次第に低下を示した．

8) 二次性脳圧上昇或いは浮腫のみられた例では両半球共に細胞密度の減少がみられたが，二次性脳圧上昇の無かつた例では，圧迫側のみの細胞密度減少しかみられなかつた．

9) 実験的頭蓋内血腫では，一次性の脳圧上昇は血腫により起される．脳圧は次いで脳の代償作用により減少するが，脳浮腫の伝播と共に，二次性に上昇する．代償期には酸素分圧は Critical level 以上に回復しており，二次性の脳圧上昇が起る前に早期手術が望ましい．

稿を終るに臨み，終始御懇篤なる御指導を戴いた半田 肇教授，先輩石川 進氏，青柳 実氏及び御協力いただいた教室各位に深甚なる感謝を捧げる．

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