SYMPOSIUM ABSTRACTS

Cerebral Circulation and Metabolism.
Sixth International CBF Symposium

MARIOTT MOTOR HOTEL, PHILADELPHIA, PENNSYLVANIA, JUNE 6-9, 1973

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We are particularly pleased to honor three men who have made major contributions to our understanding of the cerebral circulation, whose work has served as a stimulus for the present generation of cerebral blood flow investigators.

Seymour S. Kety
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Louis Sokoloff
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Session I: Autoregulation

WEDNESDAY (9:00 TO 10:45 A.M.)

CHAIRMAN: N. ZWETNOW
CO-CHAIRMAN: E. HAGGENDAL

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The Lower and Upper Limit for Autoregulation of Cerebral Blood Flow—Strandgaard S (Bispebjerg Hospital, 2400 Copenhagen, Denmark)

Autoregulation of cerebral blood flow (CBF) was studied in hypertensive and normotensive man by means of the arteriovenous oxygen difference (AVO₂) method. Blood pressure was elevated by angiotensin infusion and reduced by trimethaphan infusion combined with head-up tilt. In all patients autoregulation was demonstrated by a constant cerebral AVO₂ under moderate blood pressure changes above and below the resting pressure level. In the untreated hypertensive patients, the lower blood pressure limit of autoregulation and the brain hypoxia limit was shifted upward in correlation with the clinical blood pressure level. In some patients with normal blood pressure under effective antihypertensive therapy an almost normal lower limit of autoregulation and brain hypoxia limit was found. It is suggested that the shift upward of the autoregulation curve in untreated severe hypertension is caused by adaptive hypertrophy of the arteriolar walls, and that this abnormality is to some extent reversible with gradual blood pressure reduction.

In some hypertensive patients an upper limit of autoregulation of about mean arterial pressure (MABP) 160 mm Hg was seen beyond which AVO₂ decreased corresponding to a rise in CBF up to 160% of the resting value. Other patients tolerated MABP up to 200 mm Hg without any change in CBF. No patients showed vasospasm with decreased CBF.

The upper limit of autoregulation was further studied in the baboon in cooperation with Harper and his group in Glasgow. Bilateral CBF measurement was performed with intracarotid 133Xe injection. The lightly anesthetized baboons had a resting MABP of 80 to 100 mm Hg, and autoregulation was operating up to an MABP of 125 to 140 mm Hg. Beyond this upper limit a rise in CBF up to 200% of the resting value was consistently obtained. Some of the hemispheres studied were sympathectomized, but this had no observed influence upon the upper limit of autoregulation.

The demonstration of an upper limit of autoregulation is probably important for the understanding of the pathogenesis of hypertensive encephalopathy.

1-2


In previous studies it has been shown that blood-brain barrier (BBB) damage occurs in some types of blood pressure elevation. It also has been demonstrated that the cerebral blood flow increases when the arterial blood pressure is sufficiently elevated, i.e., when the upper limit of the autoregulatory range is surpassed. Some of these findings were discussed at the International Cerebral Blood Flow Symposium in Rome in 1971, and the flow increase that was encountered during the blood pressure increase was characterized as "break through."

The present study concerns the connection between BBB and the flow increase. It is most likely that BBB damage is the result of the post-arteriolar pressure increase, which follows an arterial blood pressure elevation above the autoregulatory range.

The present study was performed in eight anesthetized dogs. Intra-arterial injections of radioactive Krypton were used for flow measurements and the fast main component of the extracranially recorded elimination curve was used. Evan’s blue was injected intravenously before the blood pressure elevation. In some cases double-indicator technique was used for studying the BBB function after restitution of normal blood pressure. In four of the dogs there was a flow increase at high blood pressure and all of these animals showed extravasation of Evan’s blue. BBB damage also could be demonstrated when normal blood pressure was restored and thus autoregulation again was functioning. In all cases the extravasation of Evan’s blue was localized with most tracer exudation in the parieto-occipital region; in three with such signs of BBB damage there was no general loss of autoregulation, but appearance of an additional fast component, which will be discussed in another paper at this Symposium. In one dog in which such a peak phenomenon was found, there was, however, no sign of extravasation of Evan’s blue.

1-3

Effects of Local Increases of Venous Pressure on Canine Cerebral Hemodynamics—Emerson TE Jr, Parker JL (Department of Physiology, College of Human Medicine, Michigan State University, East Lansing, Michigan 48823)

Several vascular beds exhibit an increase in precapillary resistance and decrease in blood flow when venous pressure is elevated, thereby limiting the increase in capillary hydrostatic pressure which occurs. The present study was undertaken to characterize this "venous-arteriolar response" in the cerebral vasculature. Cerebral blood flow (CBF) was measured from the cannulated sinus confluens after occlusion of the transverse sinuses in anesthetized dogs. Cerebral vascular resistance (CVR), cerebral venous pressure (CVP), cerebrospinal fluid pressure (CSFP), and mean aortic blood pressure (MABP) were determined also. CVP was increased by graded elevation of the tip of the outflow cannula. CVP was measured at the point of cannulation of the sinus confluens. In the same animals, CBF autoregulation was evaluated by decreasing the cerebral pressure gradient (ΔP) through graded hemorrhage. Increasing CVP sequentially from an average value of 2.5 to 8.4, 21.7, and 27.9 mm Hg, respectively, was associated with progressive increases in CVR and decreases in CBF with no change in MABP. The maximum increase in CVP (1,116%) decreased cerebral ΔP by 22% and evoked a 100% increase in CVR and a 60% decrease in CBF; CSFP increased from a control value of 7.6 mm Hg to
a maximum of 16 mm Hg (111%). On the other hand, decreasing cerebral ΔP by 31% in the same dogs by decreasing MABP produced a decrease in CVR and CBF of 14% and 19% respectively. These data show that increasing CVP locally elicits an increase in CVR which is most probably due to active vasoconstriction, since it is well established that increasing CSFP to higher levels than in the present study does not affect CBF. Additionally, it is proposed that the constrictor response was most likely precapillary since the increase in CSFP was approximately only one-tenth as great as the increase in CVP. This latter observation suggests that capillary hydrostatic pressure only increased moderately in the face of the very large increase in CVP. It is concluded that the cerebral vasculature exhibits the "venous-arteriolar response" and that this response most likely functions to help maintain capillary pressure at a constant level. (Supported by NIH Grant HL14774.)

I-4 The Effect of Lowered Cardiac Output on Cerebral Blood Flow—Rappaport H, Bruce D, Langfit T (Division of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania)

The purpose of these experiments was to investigate the effect of decreased cardiac output on the autoregulatory capacity of the cerebrovascular bed with the thought that the vessels might not autoregulate to a simultaneous decrease in both arterial blood pressure and cardiac output, a common occurrence in heart failure, cardiac arrhythmias, and other circumstances. In ten dogs CBF was measured continuously using a toroidal outflow technique. Brains were weighed at the completion of the experiments, and CBF was estimated in ml/100 gm per minute in order to calculate metabolic data. Cardiac output was measured by a thermal dilution technique in which a known volume of cold saline is injected into the descending aorta, and cardiac output is calculated from the area under the thermal dilution curve using an appropriate computer program. Cardiac output was reduced by bipolar pacing of the heart through a transvenous catheter in the right ventricle. Cerebral autoregulation was tested before and after each ten-minute period of cardiac stimulation, and data were included in the results only if autoregulation remained intact. In preliminary experiments it was determined that an increase in the heart rate of 200 in excess of the baseline heart rate (average 170 beats per minute) was required to produce a consistent fall in cardiac output. Cardiac output fell from 2.72 ± 1.01 liters to 2.06 ± 0.78 (SD) liters (p < 0.05) during stimulation. CBF changed from 42.3 ± 11.0 to 38.0 ± 9.8 (SD) ml/100 gm per minute (NS). CMRO₂ and CMRgluoaw did not change. Mean arterial blood pressure fell from 94 to 75 mm Hg. We concluded that cerebral autoregulation maintains CBF within the normal range during moderate falls in cardiac output and arterial blood pressure produced by ventricular tachycardia.

I-5 Autoregulation of Cerebral Blood Flow During Controlled Hypotension—Fitch W, Ferguson GG, Sengupta D, Garibi J (Divisions of Neuro-anesthesia and Neurosurgery, Institute of Neurological Sciences, Southern General Hospital, and The Wellcome Surgical Research Institute, Glasgow, Scotland)

The effect of graded progressive hypotension on the cerebral circulation has been studied in anesthetized baboons. Cerebral blood flow has been measured following the intracarotid injection of 133Xenon and by electromagnetic flow probe on the common carotid artery. Progressive hypotension has been produced over a period of four to five hours, either by graded hemorrhage or by the administration of increasing concentrations of hypotensive drugs. The drugs investigated have included halothane, halothane plus sodium nitroprusside, and halothane plus trimethaphan camphorsulphonate. Subsequently, a further group of animals has been subjected to hemorrhagic hypotension under conditions of α-adrenergic blockade, produced by the prior administration of phenoxybenzamine (1.5 mg per kilogram).

In all animals, controlled measurements of cerebral blood flow were made under nitrous oxide/oxygen/analgic anesthesia. In those animals subjected to hemorrhagic hypotension blood was withdrawn from the femoral artery in quantities sufficient to lower the mean arterial blood pressure in steps of approximately 10 mm Hg. Cerebral blood flow was determined at each step reduction. In the other animals, increasing concentrations of the drug(s) under study were given to reduce mean arterial blood pressure by 10 mm Hg decrements.

Mean control values between all groups of animals showed no marked differences. During hemorrhagic hypotension, autoregulation was maintained until a mean arterial blood pressure of approximately 65 mm Hg had been reached, after which the cerebral blood flow was pressure passive. With drug-induced hypotension, autoregulation persisted to lower levels of mean arterial blood pressure (approximately 35 mm Hg) although there were slight variations between the different drugs studied. Under α-adrenergic blockade, animals subjected to hemorrhagic hypotension showed a persistence of autoregulation to levels similar to those obtained with drug-induced hypotension.

It is postulated that under conditions of hemorrhagic hypotension, constriction of the extraparenchymal cerebral vessels in response to sympathetic stimulation decreases the possible range of autoregulation in the anesthetized baboon.

(The studies reported here were undertaken as part of the work of the Medical Research Council's Unit for Research into the Cerebral Circulation. Directors: W. B. Jennett and A. M. Harper.)


Deep profound hypotension (<25 mm Hg) very quickly causes ischemic lesions in boundary zones and abolishes CBF autoregulation. We have studied the effects on CBF autoregulation and CSF acid-base parameters of a severe degree of induced hypotension which, however, is
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employed clinically. We produced the hypotension with deep halothane anesthesia since Nilsson and Siesjo have suggested that the associated lowering of cerebral metabolism may protect the brain from ischemia.

Eleven baboons anesthetized with N2O/O2 and halothane (0.5%) were artificially ventilated to normocapnia and their body temperature was maintained at 37°C. Hypotension was induced by increasing the inspired halothane concentration until MBP fell to 33 mm Hg. It was kept at this level for 70 to 187 minutes. During hypotension (1) CBF, measured by Xenon clearance and a carotid electromagnetic flowmeter (external carotid circulation tied off), fell by more than 50%. (2) sagittal sinus oxygen saturation was 46%, and (3) CMRO2 decreased from 5.15 to 3.56 ml/100 gm per minute at this deeper level of anesthesia. After hypotension cerebral hyperemia occurred in those animals which regained an MBP of 70 mm Hg or more. CBF autoregulation was tested by I.V. infusion of norepinephrine in six baboons. In four autoregulation was present before hypotension. In all it was absent or impaired afterward. Acid-base measurements on CSF collected anaerobically from the cisterna magna showed that CSF bicarbonate did not change, i.e., that no CSF metabolic acidosis developed during or after hypotension to account for the loss of autoregulation.

I-7 Correlation of Regional Cerebral Blood Volume With PaCO2 and Arterial Blood Pressure—Phelps ME, Grubb RL Jr, Raichle ME, Ter-Pogossian MM (Washington University, St. Louis, Missouri)

The regional cerebral blood volume (rCBV) was measured in Rhesus monkeys in vivo by stimulated x-ray fluorescence of the iodinated radiographical contrast material, Renografin-76®. The Renografin-76® was injected intravenously and the amount of contrast material per volume of cerebral tissue and the amount per volume of blood were measured by stimulated x-ray fluorescence. This provided a three-dimensionally regional, noninvasive (I.V.) measure of rCBV which required only one minute. The accuracy of the method in Rhesus monkeys has been shown to be ~±4% from phantom studies and in vivo and in vitro comparisons. For a control and to demonstrate the reproducibility of the method, a Rhesus monkey was held at a constant arterial CO2 pressure (PaCO2) of 37 mm Hg and rCBV measured at 8, 16, 25 and 43 minutes. The values of rCBV were observed to remain constant within the error of the method (~±4%). The rCBV was measured over a PaCO2 range of 19 to 92 mm Hg in seven lightly anesthetized and paralyzed Rhesus monkeys. The PaCO2 was varied by passive hyperventilation and hypoventilation and by administering a mixture of 5% CO2 and 95% O2. Measurements were made at five levels of PaCO2 in each animal. The rCBV changed from 4.9 to 8.3 cc/100 gm over this PaCO2 range and a linear relationship between rCBV and PaCO2 (rCBV = 0.046 ±0.001 SD) PaCO2 + 4.06) was found at a confidence level of P < 0.001 (n = 35, r = 0.94). A significant correlation also was found between CO2 responsivity of rCBV (slope of above equation) and mean arterial blood pressure (P < 0.02). In a second series of experiments the rCBV was measured as a function of mean arterial blood pressure (MABP). At a constant PaCO2 the rCBV was observed to decrease with increases in MABP and vice versa, thus demonstrating autoregulation in terms of the cerebral blood volume. Hyperemia was observed following restoration of MABP when autoregulation had been exceeded. An inverse linear relationship between rCBV and MABP (rCBV = -0.015 ±0.004 SD] MABP + 6.26 ([± 0.47 SD]) was found at a confidence level of P < 0.001 (n = 33, r = -0.6) over an MABP range of 35 to 200 mm Hg.

These studies demonstrate that rCBV measured in this manner may be useful in noninvasively and regionally evaluating cerebral hemodynamics.

RESERVE CBF and Metabolism With Regard to Autoregulation in Cerebral Perfusion Pressure Experiments—Hoyer S, Hamer J, Stockel H, Alberti E (Institut für Pathochemie und Allgemeine Neurochemie der Universität Heidelberg, Heidelberg, West Germany)

In ten dogs global CBF (Kety-Schmidt technique), cerebral uptake of oxygen and glucose, and cerebral output of CO2 and lactate were measured to study the relationships between CBF and cerebral AV-substrate differences, to look for signs of metabolic autoregulation of CBF and cerebral hypoxia, respectively.

The stepwise decrease of cerebral perfusion pressure (CPP) was performed by lowering the mean arterial pressure pharmacologically under normocapnic (mean PaCO2 36 mm Hg) and normovolemic conditions. Under steady state conditions measurements were carried out at a mean CPP of 98 (stage 1), 71 (stage 2), and 42 (stage 3) mm Hg, respectively. In this low pressure state the responsiveness of CO2 on CBF and metabolism was investigated (stage 4: mean PaCO2 82 mm Hg, CPP 43 mm Hg).

When CPP was lowered from mean 98 to 71 mm Hg, we found no statistical differences in regard to blood flow, AV differences of oxygen and glucose, although the mean AV difference of glucose rose from 7.7 mg % to 9.1 mg % and the CMRglucose from 4.6 to 3.6 mg/100 gm per minute, respectively, when going from stage 1 to stage 2. On the other hand, we measured a significant increase of cerebral CO2 release and lactate production from stage 1 to stage 2, which was 5% in stage 1 and 26% in stage 2, related to the amount of glucose taken up by the brain. The cerebral energy state did not change between stages 1 and 2. A statistically significant drop of CBF occurred at a mean CPP of 42 mm Hg (stage 3). The AV difference of oxygen (not significant) and the AV difference of glucose (significant) rose, while both metabolic rates fell significantly. The AV difference of CO2 did not increase any more and the CMRCO2 decreased significantly. The AV difference of lactate rose from 2.1 to 3.8 mg % (stages 2 to 3, not significant), but this was only a 30% lactate production with regard to the glucose uptake. CMRlactate did not change and the cerebral energy state decreased only a little in stage 3. In stage 4 the responsiveness of CO2 on CBF and metabolism at a low CPP (mean CPP 43 mm Hg) was studied. By means of

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elevation of \( P_{aO_2} \) from normocapnic values to mean 82 mm Hg, CBF increased significantly to the normal range and so did AV differences of oxygen and AV differences of \( CO_2 \) as well as CMRox and CMR\( CO_2 \). On the other hand, AV differences and metabolic rates of glucose and lactate dropped significantly as well as the cerebral energy state.

These results lead to these conclusions: (1) A drop of cerebral perfusion pressure from normal to about 70 mm Hg does not influence CBF and the oxidative metabolism of the brain. The constancy of CBF and cerebral metabolic rates could not be held up at low CPP values. (2) The cerebral overproduction of lactate (lactacidosis) during stepwise lowering of CPP is related to a surplus of glucose extraction from the arterial blood. Glucose is the only source from which lactate derives. (3) Lactacidosis in low cerebral perfusion pressure is no sign of cerebral hypoxia but a proof of the metabolic regulation of CBF. The formation of an "excess" lactate due to low CPP leads to a liberation of \( CO_2 \) out of the cerebral bicarbonate reserve, so that CBF can be kept at a constant level in a wide pressure range. When the cerebral bicarbonate reserve is exhausted, CBF decreases as well as cerebral metabolism.

**SUMMARY:** N. Zwetnow

**Session II: Chemical Control**

**WEDNESDAY (11:00 A.M. TO 12:45 P.M.)**

**CHAIRMAN:** J. Severinghaus

**CO-CHAIRMAN:** O. Paulson


Changes in intravascular hydrogen ion concentration are believed to have little direct effect upon cerebral blood flow. While acute metabolic alkalosis produced by sodium bicarbonate infusion has been shown to produce transient increase in cerebral blood flow in animals and in man, this has been ascribed to transient associated increase in \( P_{aCO_2} \), acting via the \( CO_2 \) shuttle to lower periarteriolar extracellular fluid pH.

Studies in this laboratory have examined the effect of metabolic alkalosis upon cerebral blood flow when \( P_{aCO_2} \) was controlled, to eliminate transient alterations. Studies in man have been completed during moderate (\( P_{aCO_2} = 20 \) torr) and mild (\( P_{aCO_2} = 30 \) torr) respiratory alkalosis. Metabolic alkalosis was produced by infusion of 5.5 m moles NaHCO\(_3\) per kilogram of body weight in 17.9 ml H\(_2\)O per kilogram of body weight over a one-hour period during which \( P_{aCO_2} \) was controlled at a constant level. With \( P_{aCO_2} \) controlled near 20 torr, bicarbonate infusion was associated with increased cerebral blood flow in each of six subjects, the average increase of 17% being significant (\( P < 0.01 \)). With \( P_{aCO_2} \) controlled near 30 torr, bicarbonate infusion was associated with slight increases of cerebral blood flow in three subjects and slight decreases in three with no average change.

We ascribed these differences to the effect of metabolic alkalosis upon oxygen transport (Bohr effect). The level of baseosis achieved in this study (base excess = 12 mEq/L) shifts the oxygen dissociation curve 5 torr to the left. CBF of half normal, achieved by hypocapnia (\( P_{aCO_2} \) 20 torr), produced borderline cerebral hypoxia. Metabolic alkalosis produced full-scale hypoxia and caused cerebral vascular dilation and increased blood flow when \( P_{aCO_2} \) was 20 torr. This occurred due to tissue hypoxia secondary to reduced oxygen availability resultant from the Bohr effect. At \( P_{aCO_2} \) 30 torr, a 5-torr shift to the left of the hemoglobin dissociation curve would not be expected to produce cerebral tissue hypoxia. This theory was supported by metabolic measurements showing more marked increase in CMR\( \text{met} \) at \( P_{aCO_2} \) 20 torr than at 30 torr. The current series measured the effect of metabolic alkalosis upon cerebral blood flow at normocapnia. Using identical experimental design, arterial \( P_{aCO_2} \) was controlled near 40 torr throughout. After control measurement of cerebral blood flow, sodium bicarbonate was infused as base. Cerebral blood flow increased in seven of eight subjects, with a mean increase of 27% (\( P < 0.05 \)).

The increase in CBF following bicarbonate infusion at \( P_{aCO_2} \) 40 torr was not expected. Since \( P_{aCO_2} \) was unchanged following NaHCO\(_3\) infusion, an increase in CBF is hard to explain.

Cerebral vessels have been shown to be sensitive to osmotic load. Plasma hyperosmolality secondary to NaHCO\(_3\) infusion might be expected to produce some degree of cerebral vasodilation. However, if osmotic dilation did occur when \( P_{aCO_2} \) was 40 torr, it is difficult to explain failure of osmotic dilation at \( P_{aCO_2} \) 30 torr.

Another possible explanation for different results at \( P_{aCO_2} \) 30 torr and \( P_{aCO_2} \) 40 torr might be that at very high concentrations of (H\(_2\)CO\(_3\)) and \( CO_2 \) in plasma, some \( CO_2 \) leaks through the blood-brain barrier, lowering cerebral tissue or periarteriolar pH and thus dilating cerebral vessels.

II-9 Circulation to the Brain of Rats During Acute and Prolonged Hypcapnia and Hypocapnia—Pannier JL, Leusen I (Laboratory of Normal and Pathological Physiology, University of Ghent, Ghent, Belgium)

There are only a few studies where cerebral blood flow (CBF) was measured at multiple \( P_{aCO_2} \) levels during prolonged alterations in the acid-base balance. A quantitative correlation between CBF and the pH of the cerebrospinal fluid was attempted in chronic metabolic acidosis and alkalosis in conscious human volunteers. In the present experiments CBF was studied at different acutely induced \( P_{aCO_2} \) levels in control rats and in rats kept for 24 hours before the experiment in 10% \( CO_2 \) in air (prolonged hypercapnia) or in 10% \( O_2 \) in \( N_2 \) (hypoxic hyperventilation producing hypocapnia). \(^{141}\)Ce-labeled microspheres with a diameter of 15 ± 5 μ were injected into the left heart ventricle to study the fractional distribution of the cardiac output to the
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Brain. In some animals the cardiac output was measured with the same method using a known reference flow collected at a constant rate from a femoral arterial catheter. The curve relating the flow fraction to the brain and the $P_{\text{Pa}}$, is shifted upward and to the left after 24 hours of hypoxic hyperventilation, and downward and to the right after 24 hours of hypercapnia. A similar shift is observed after alpha adrenergic receptor blockade (phentolamine).

Changes in the flow fraction to the brain are essentially due to modifications of the CBF, since the cardiac output was not significantly influenced by acute or prolonged alterations in the $P_{\text{Pa}}$.

When the results are plotted as a function of the "composite" brain pH, the CBF seems to vary as a single function of this parameter in the three different groups of animals.

II-10 Primiate Pial Arterial Pressure Responses to Changes in Inspired CO₂ and Systemic Arterial Pressure—Stromberg DD, Fox JR (Microcirculation Laboratory of the Department of Physiology and Biophysics and the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington 98195)

Pial arteries were exposed by trephination in 22 pentobarbital-anesthetized squirrel monkeys, and the vessels and surrounding parietal cortex were continuously bathed in warmed, pH-buffered artificial CSF (Elliot's B solution). Blood pressure was measured in 28 pial arteries and arterioles ranging in diameter from 10 μ to 260 μ with glass micropipets using the servo-nulling technique. Systemic arterial pressure ($P_A$), venous pressure ($P_V$), and respiratory end-tidal CO₂ were measured continuously and arterial blood $P_{\text{Pa}}$, $P_{\text{p}}$, and pH were sampled intermittently. Sequential pressure measurements in branches of the same pial arterial network yielded differences between pressure in the smallest (10 to 25 μ) and in the largest (260 μ) vessels of only 5 to 15 mm Hg (80 ≤ $P_A$ ≤ 100 mm Hg), suggesting a restricted role for this portion of the microvasculature in control of total cerebral blood flow. When systemic arterial pressure was varied from 40 to 120 mm Hg by withdrawal or reinfusion of arterial blood, pial artery pressure ($P_{\text{p}}$) was a linear function of systemic pressure. Furthermore, the value of ($P_{\text{p}} - P_A$) / ($P_{\text{p}} - P_V$) always increased for decreasing systemic arterial pressure, suggesting a relative dilation of parenchymal vessels. Increased CO₂ concentrations of 5% and 10% yielded pial artery pressure decreases with smaller changes at lower systemic pressures. Since a relative dilation of parenchymal vessels probably occurred with decreased systemic pressure, it is likely that the diminished CO₂ response at low systemic pressure represented a slight additional dilation of the parenchymal vasculature. (Supported in part by NIH Grants HL10861, HL14777 and GM01160.)

II-11 Dual Control of Cerebral Circulation. Separate Sites of Action in Vascular Tree in Autoregulation and Chemical Control—Gotoh F, Muramatsu F, Fukuuchi Y, Amano T (Department of Neurology, Keio University, Tokyo, Japan)

The mechanism of the autoregulation of the cerebral circulation has been a subject of controversy. Also, it is still being debated whether autoregulation and chemical control of the cerebral circulation are mediated by an identical mechanism. In the last communication of this Symposium, we reported the dissociation of autoregulation and chemical control in patients with Shy-Drager syndrome (a loss of autoregulation without impairment of chemical control), and suggested the role of the autonomic nervous system in the autoregulation.

The observations in these patients also suggest the hypothesis that the size of arteries functioning in autoregulation should be different from that in chemical control, because it is well accepted that as the diameter of the pial arteries diminishes, so the density of the innervation falls.

To verify this hypothesis, the following experiment was performed. Cats were anesthetized with pentobarbital, and were immobilized with d-tubocurarine. The respiration was controlled using the respirator. The skull was opened, and the brain surface was covered with mineral oil. The influences of autoregulation and chemical control on the diameter of pial arteries (15 to 200 μ in diameter) were examined by means of photography. Exsanguination and reinfusion of the blood were employed as a means of altering the perfusion pressure. CO₂ inhalation and hyperventilation also were used for changing $P_{\text{Pa}}$.

The changes after exsanguination or reinfusion were more pronounced in arteries with a diameter of more than 50 μ, while the changes of the diameters during CO₂ inhalation or hyperventilation were apparent in arteries with a diameter of less than 50 μ. In other words, the arteries functioning in autoregulation are the larger ones with dense innervation, and the smaller arteries with coarse innervation are functioning in the chemical control.

The present results suggest that there is a dual control of the cerebral circulation—the neurogenic control operating in autoregulation and the chemical control functioning in cerebral vascular response to local metabolic needs, and that the sites of action of the two mechanisms are separate in the cerebral vascular tree.

II-12 Interdependence of Capillary Flow and Regional Blood Flow of the Brain—Leniger-Follert E, Lübbers DW (Max-Planck-Institut für Arbeitsphysiologie, Dortmund, Germany)

Microflow measurements by means of electrochemically generated hydrogen impulses according to Stosseck and Lübbers (1970) permitted us to obtain information of the blood flow in the capillary range of the brain. The results given below show that there is a different interdependence of regional blood flow (measured after intra-arterial injection of $^{133}$Xe according to Ingvar and Lassen) and of microflow (measured with the hydrogen method).

(a) Under normal physiological conditions, regional blood flow through the gyrus suprasylvius of the cat showed a homogeneous behavior with respect to time and localization. In the range of individual capillaries, however, the blood flow values varied between 0 and 591 ml/100 gm x min with an arithmetic mean of 158.9
ml/100 gm x min ± 121.9. At five-second intervals the capillaries were observed to open and to close.

(b) In the case of anoxia this capillary play ceased. Ten to 15 seconds after the beginning of anoxia blood flow through the capillaries strongly increased.

(c) Capillary and regional blood flow changed in the same way, when respiring the animal with a gas mixture containing increasing quantities of CO₂. Then, as a rule, an increase in both regional and local blood flow was observed. Sometimes, however, local blood flow might remain relatively constant, although CO₂ concentration was changed.

(d) Stepwise increase of the mean arterial blood pressure yielded (for regional blood flow) the so-called autoregulatory reaction, while sometimes microflow showed a linear increase in blood flow.

(e) The capillary play was considerably reduced by intravenous injection of papaverine.

When using measuring electrodes with larger diameters (50 to 100 μm), the measurements average over the supply area of several capillaries. These electrodes do not monitor the capillary play, but an average blood flow value close to the regional blood flow measured by Xenon.

The experiments showed that, under normal conditions, brain tissue is not homogeneously perfused. We assume that the locally changing flow is regulated by the local metabolic activity.

### II-13 Interactions of Ionic Mechanisms in the Regulation of the Resistance of Pial Vessels—Betz E. Enzenross HG, Vlahov V (Institute of Physiology [I], Tuebingen, West Germany)

Local control of pial arteries and arterioles is strongly influenced by the ionic milieu in the immediate vicinity of the smooth muscles. In microperfusion experiments with mock-CSF increases of the H⁺ ion concentration in the extravascular space cause dilatations and decreases of H⁺ constrictions of the vascular diameter. The H⁺-caused dilatation, however, can be reduced by increases of Ca⁺⁺ in the extravascular space. Increases of extravascular K⁺ up to twofold of normal values lead to dilatation of pial arteries and arterioles, whereas higher concentrations cause constrictions.

The variations of the ionic milieu were combined with electrical stimulation of the wall of pial vessels. For stimulation we used micro-electrodes. The different electrode had a diameter of about 80 μm; the indifferent electrode was T-shaped. The electrodes were directly attached to the outside of the vessels. A stimulation period of ten seconds with 5 mA always causes constriction in normal vessels and in vessels previously dilated by application of mock-CSF with low pH or by high CO₂ in the respiratory gas. The constritory effect of electrical stimulation is partially prevented by EDTA and is completely abolished with EGTA in the extravascular space. This effect is independent on the pH of the CSF. If calcium-free CSF is applied, a constriction still can be observed.

It is concluded that in the constriction of vessels at least two different mechanisms are involved. (Supported by the Deutsche Forschungsgemeinschaft.)
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parameters were calculated: (1) total cerebral blood flow (CBF), (2) total cerebral blood volume (CBV), and (3) mean transit time (t). Cerebrovascular resistances were calculated by the following formulas:

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(1) \text{total resistance } R_t = \frac{\text{MABP} - \text{MJVP}}{\text{CBF}},
\]

\[
(2) \text{subarachnoid venous resistance } R_s = \frac{\text{SSWP} - \text{MJVP}}{\text{CBF}},
\]

and (3) arterial resistance \((R_a = R_t - R_s)\). Autoregulation was tested by elevating the MABP with angiotensin amide or blood replacement and lowered by graded hemorrhage. Autoregulation and \(\text{CO}_2\) reactivity were tested before and after the animals were rendered hypoxic (cerebral venous Po \(20 \text{ mm Hg}\)) until the EEG became isoelectric and then restored on 21% \(\text{O}_2\).

Autoregulation is typified by the following: (A) a constant \(\text{PP-R}_a\) slope of circa 0.01 which is independent of the method of \(\text{PP}\) manipulation in the intact animal, (B) it is constant through a \(\text{PP}\) range of circa 60 through 150 mm Hg and not significantly changed by \(\text{Pa}_\text{CO}_2\) elevations up to 70 mm Hg, (C) it is completely, but reversibly, inactivated by hypobaric (X 21 mm Hg).

The typical posthypoxic alterations are: (1) a persistent reduction in arterial resistance, (2) a marked impairment of arteriolar reactivity (autoregulation) to pressure, (3) loss of \(\text{CO}_2\) reactivity, and (4) increased cerebral blood volume.

SUMMARY: J. Severinghaus

Session III: Focal Lesions I

WEDNESDAY (2:00 P.M. TO 3:45 P.M.)

CHAIRMAN: A. WALTZ
CO-CHAIRMAN: A. AGNOLI

III-15 Cerebral Edema Due to Cerebral Infarction in the Gerbil—Harrison MJG, Ross Russell RW (Institute of Neurology, National Hospital for Nervous Diseases, Queen Square, London, WC1N 3BG, England)

It is known that the circle of Willis in the Mongolian gerbil lacks a major posterior communicating artery and that unilateral ligation of the common carotid artery under barbiturate anesthesia is followed by infarction of the ipsilateral hemisphere in 60% of animals. Infarction produces neurological deficit and death in 90% of instances.

In a series of animals eight hours after carotid ligation, the cerebral hemispheres were removed and the water content of each hemisphere measured by a comparison of wet and dry weights. After ligation an increase (more than 6% "swelling percent") in water content of the ipsilateral hemisphere was found in 14 (70%) of a group of 20 animals. Twelve of the 14 showed neurological deficit during life.

Intraperitoneal dexamethasone (5 mg/kg) given immediately after carotid ligation and again 24 hours later reduced the morbidity and mortality from 60% to 20% \((P < 0.01)\), and given at the time of surgery reduced the proportion of animals developing marked edema from 70% to 30% \((P < 0.05; n = 20)\).

A slow intravenous injection of trypan blue was used to stain the capillary endothelium and to indicate capillary patency. After carotid ligation there was a small difference in capillary staining between the two hemispheres in four of 20 animals. In another group of animals injected eight hours postoperatively complete absence of staining was found macroscopically on the affected side in ten of the 20 animals. Studies of hemisphere perfusion using a diffusible indicator (+C amidopyrine) showed that the reduction in perfusion on the affected side was greater eight hours after surgery than immediately postoperatively.

Cerebral infarction and necrosis of the gerbil is accompanied by edema which takes some hours to develop and which may be responsible for secondary changes in blood flow by obliteration of the capillary bed. The reduction in morbidity and mortality afforded by dexamethasone may be due to its effects on cerebral edema and consequently on blood flow.

III-16 Development and Resolution of Edema in Experimental Cerebral Ischemia and Infarction—O’Brien MD, Waltz AG (Cerebrovascular Clinical Research Center and the Department of Neurology, University of Minnesota, Minneapolis, Minnesota 55455)

The left middle cerebral artery (MCA) was approached transorbitally in 26 anesthetized cats and occluded in 22. Four hours to 20 days later sodium pertechnetate (technetium-99m), sodium-22 chloride, and albumin labeled with iodine-131 were injected intravenously; the circulation was stopped with KCl; and the brain was removed quickly, frozen, and sliced coronally at the tips of the temporal lobes. Sixteen samples of brain tissue weighing 30 to 50 mg were taken from each hemisphere from regions normally supplied by the MCA. Wet and dry weights were obtained for each sample; water content was expressed as percent of wet weight. The uptake of each radioactive indicator was expressed for each sample as the ratio between the count rate per unit wet weight of the brain sample and the count rate per unit weight of a sample of blood taken one minute before the circulation was stopped. In cats with an occluded MCA samples from the right hemisphere were considered "nonischemic;" categorization of samples from the left hemisphere as "ischemic" or "infarcted" was based on microscopic examination of adjacent histologic sections.

In cats with sham operations there were no differences in water content or uptake of radioactive indicators among the samples from the two hemispheres. In each cat with an occluded MCA water content was greatest in infarcted and least in nonischemic tissue. However, the water content of all three categories of tissue was increased at one, two, and three days after occlusion, reaching a maximum at two days. At five, seven, ten, and 20 days water content was less than at earlier times and relatively constant. The uptake of the radioactive indicators was relatively constant in nonischemic tissue. In infarcted and ischemic tissue the uptakes of pertechnetate and albumin were maximal at three to five days and the uptake of sodium was maximal at one to two days after MCA occlusion; at later times uptakes remained

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increased despite the relatively decreased water content. At four days the ratio of uptake of pertechnetate between infarcted and nonischemic tissue was maximal (8.8) but a substantial "lesion/background" ratio (4.8) was present as early as 15 hours after MCA occlusion.

Thus, unilateral occlusion of an MCA in cats causes bilateral cerebral edema that is transient and more pronounced in infarcted and ischemic regions. The distributions of pertechnetate, albumin and sodium are not related solely to ischemic cerebral edema but may be affected by disruptions of endothelial and cellular structures.

(Supported in part by Research Grant NS 3364 from the National Institutes of Health, U. S. Public Health Service. Dr. O'Brien is the recipient of an International Post-Doctoral Research Fellowship from the National Institutes of Health, U. S. Public Health Service.)

III-17
Cerebral Blood Flow in Baboon Following Carotid Ligation: Effects of Hypoxia and Hypotension—Sengupta D. Harper AM, Jennett WB (MRC Cerebral Circulation Research Group at the Wellcome Surgical Research Institute and the Institute of Neurological Sciences. The University of Glasgow)

Following carotid ligation, the risk of ischemia in the ipsilateral cerebral hemisphere is always present. Although neurological complications may occur immediately following carotid ligation, more often there is a delay in the development of a neurological deficit. The reason for this delayed ischemia is not known. In a previous paper we showed that following carotid ligation in the baboon, cerebral blood flow (CBF) to the ipsilateral hemisphere did not alter significantly. Nevertheless, there was a marked reduction in the CBF response to hypercapnia.

In the present study we investigated the changes in CBF in the baboon in response to hypoxia and hypotension following ipsilateral carotid ligation.

CBF in the anesthetized baboons was measured from the right hemisphere following intracarotid injection of 133Xe, using ten-minute height/area technique. Arterial BP, Pao2, and Pao2 were monitored. The animals were kept normocapnic (Paco2 ~ 40 mm Hg).

In five baboons, following estimation of CBF at normal Pao2, hypoxia was induced by reducing the inspired oxygen concentration. At hypoxia (mean Pao2 = 38.5 mm Hg) CBF was increased by 81%. This sequence was repeated after the right carotid artery ligation. Following the ipsilateral carotid ligation, at normal Pao2 there was no change in CBF, but during hypoxia (mean Pao2 = 41 mm Hg) CBF increased by only 20%.

In another series of ten baboons, after control CBF estimations, the right carotid artery was ligated. The animals were then rendered progressively hypotensive by hemorrhage until the mean arterial blood pressure (MABP) was reduced to 20 to 30 mm Hg. CBF was measured at each step reduction in the MABP. Results showed that following carotid ligation, CBF in the ipsilateral hemisphere diminished pari passu with the fall in MABP. In other words, the autoregulation of CBF in the face of lowering of MABP was defective.

It is inferred that although CBF may be normal following ipsilateral carotid ligation, it is likely that the circulatory reserve of the brain is not sufficient to meet physiological challenges such as hypercapnia, hypoxia or hypotension, and this may be the reason for the development of delayed neurological complications.

III-18
Atraumatic Transient Focal Cerebral Ischemia in Monkeys:—Crowell RM, Olsson Y (Neurosurgical Service, Massachusetts General Hospital, Boston, Massachusetts; and Patologiska Institutionen, University of Uppsala, Sweden)

After focal cerebral ischemia has caused irreversible neuronal damage, emergency therapy for ischemia is unlikely to be effective. When does such irreversible damage occur? Several previous studies addressing this question were hampered by excessive surgical trauma. Recently Hudgins and Garcia have described a transorbital microsurgical method of atraumatic middle cerebral artery (MCA) occlusion. We have utilized this technique to investigate the maximum tolerable duration of focal cerebral ischemia in monkeys.

Twenty-eight macaque monkeys were studied. Animals were anesthetized with ketamine hydrochloride (15 mg per kilogram) and pentobarbital (30 mg per kilogram). Under the dissecting microscope, the MCA was exposed, meticulously dissected free, and occluded with a spring clip. Occlusions of various durations were carried out (four hours, eight hours, 16 hours, 24 hours, permanent occlusion). Animals were reanesthetized for clip removal. Blood pressure, arterial blood gases, and hematocrit were normal in almost all cases. Clinical deficit was assessed according to a five-point grading system (O = none, 1 = mild, 2 = moderate, 3 = severe, 4 = dead). Animals were sacrificed at two weeks, and the brains were evaluated both grossly and histologically.

Thus, the extent of infarction was estimated according to a four-point grading system (O = none, 1 = less than 3 mm in diameter, 2 = larger than 3 mm confined to subcortex, 3 = subcortical and cortical).

Monkeys tolerated atraumatic focal cerebral ischemia remarkably well. Four-hour and eight-hour clipping caused little or no clinical deficit (grades 0 to 1) and usually no or small subcortical infarctions (grades 0 to 1). Sixteen-hour, 24-hour, and permanent occlusion usually led to moderate or severe deficits or even death (grades 2 to 4), and most infarcts were medium-sized or large (grades 2 to 3). Both clinically and pathologically, animals with four-hour and eight-hour ischemia differed significantly on chi-square testing from animals with 16-hour, 24-hour or permanent occlusions.

The data suggest that, in selected clinical cases, medical therapy or surgical cerebral revascularization begun as late as eight hours after the onset of focal cerebral ischemia might be followed by clinical improvement.
SYMPOSIUM ABSTRACTS

III-I9
Effect of Alpha Methyl Tyrosine on Cerebral Infarction—
Zervas NT (330 Brookline Avenue, Boston, Massachu-
setts 02215), Hori H

Cerebral infarction was induced in 26 squirrel
monkeys by intermittent occlusion of the middle
cerebral artery using a tranorbital approach. Alpha
methyl tyrosine, a norepinephrine blocker, was adminis-
tered prior to and after the occlusion of the vessel using
a double-blind method. The animals were then graded
for neurological performance and survival as compared
to a group of controls. The brains of the animals were
perfused with colloidal carbon black and light micro-
scopic histological preparations were made to assess the
adequacy of the microvasculature and histological
changes on light microscopy. Brain ATPase catechol-
amine and serotonin levels were compared for the two
groups of animals in both hemispheres and the changes
noted with respect to the time of vascular occlusion.

There was a distinct difference between the survival time
and neurological functioning of the animals treated with
alpha methyl tyrosine. The biochemical, histological and
neurological changes will be demonstrated. The relation-
ship of the beneficial effect of alpha methyl tyrosine on
cerebral infarction to the studies on spinal cord injury
pioneered by Osterholm will be discussed.

III-20
Energy Metabolites, Water Content and Catecholamine
Changes in a Model of Cerebral Embolic Infarction—
Kogure K, Busto R, Reinmuth O, Scheinberg P (Cere-
bral Vascular Disease Research Center, Department of
Neurology, University of Miami School of Medicine,
Miami, Florida)

Cerebral infarction was produced in groups of rats by
carotid injection of 35 μ microspheres and at intervals
up to four hours tissue norepinephrine (NE), 5-
hydroxytryptamine (5-HT), dopamine (DA), phospho-
creatine (PCr), ATP, ADP, AMP, glucose, glycogen,
lactate, pyruvate and water content values in embolized
and uninjured hemispheres were determined. CSF acid-
basis and lactate values and derived functions of the
variables were determined. In contrast to the report of
Sundt, marked changes in PCr, ATP, AMP, La, La/Py
and water content occurred at five minutes and tended
to recover beneficially. NE dropped at five minutes,
increased above normal at 30 minutes and returned to
normal at four hours. No significant changes were
detected in 5-HT and DA. The lesioned hemisphere
showed lesser or delayed effects. The CSF La only
significantly reflected the tissue damage.

These data show a striking capacity of cerebral
metabolism to restore normality and demonstrate the
presence of acute NE changes in embolized brain. The
model used allows consistently reproducible unilateral
infarction in the rat brain without elaborate alteration
of systemic vascular physiology and introduces a useful
advance in assessment of metabolic and catecholamine
parameters in experimental cerebral infarction more
comparable to clinical disease than has previously been
possible.

III-21
Regional Cerebral Metabolism in Experimental Brain In-
farction—Held K, Jacobsen O, Kraft K, Berghoff W

(First Medical Clinic, University-Hospital, Kiel, West
Germany)

Regional changes of CBF in local brain ischemia are
now well documented by numerous studies. Little is
known, however, about the concomitant metabolic
alterations. Information beyond whole brain or hemi-
spheric metabolism (in man) so far has had to be
derived from experimental studies. Embolic infarctions
therefore have been produced in 26 dogs, using the
technique described by Molinari. Seventeen animals
either died spontaneously or were sacrificed between
three and 60 hours for pathological examination. The
remaining nine dogs, all demonstrating neurological
symptoms, were chosen for metabolic studies 24 hours
after infarction. Under maintained circulation and
artificial respiration the whole head was immersed into
liquid nitrogen. The frozen brain was then separated
into the infarcted (1) and the perifocal (2) zones. Further
samples were taken from the same hemisphere
(3), from white (4) and gray (5) matter of the
contralateral side for evaluation of high energy
phosphates and their metabolites, glycogen, glucose and
its metabolites, and for water content. The results
obtained were compared to control values of white and
gray matter in normal dogs. Infarcted tissue was stained
by Evans blue and evidenced gross changes on
inspection.

Although a significant reduction of Creatinphosphate
(Kr-P) and ATP with concomitant changes of the
ratios Kr-P/Kr and ATP/ADP was noted in area 1,
considerable amounts of high energy phosphates were
preserved in the infarcted tissue even after 24 hours.
There was a trend of energy reduction in areas 2 and 3,
also. Distinct alterations of glucose metabolism were
observed in most of the regions studied. Significant
glucose reduction extending from area 1 to 4 was
accompanied by a significant lactate accumulation and
an elevated lactate/pyruvate ratio in these areas. A
significantly raised water content was present, likewise,
in regions 1 through 3.

The significance of our results will be discussed in
reference to: (1) the distinct differences in whole brain
ischemia, (2) the well-known findings of CBF in
cerebral infarction, and (3) pathogenetic aspects and
clinical implications.

RESERVE
Segmental Reactivity of Cerebral Vessels and Brain Damage
—Carpi A, Cartoni C, Giardini V (Department of
Therapeutic Chemistry, Instituto Superiore di Sanita,
Rome, Italy)

The intracranial vasodilation produced by histamine
(Hi) and acetylcholine (Ach) is revealed both by the
increase in intracranial venous pressure (IVP), reflect-
ing the decrease in cerebrovascular resistance, and by
the rise in CSF pressure (CSFP), reflecting the increase
in intracranial blood volume. In dogs under barbiturate
anesthesia, these changes were measured in control
conditions and after the production of an acute closed
cerebral lesion by liquid nitrogen. Control experiments
were carried out with dogs subjected to a sham
treatment. Brain damage did not modify either the
arterial hypotension or the IVP increase caused by Hi.
On the contrary, a significant increase in the CSFP response to Hi was already present 30 minutes after the treatment with liquid nitrogen and was even more evident three hours later. Arterial, IVP and CSFP responses to Ach were unaffected by the brain lesion. The enhanced desponsivity to Hi was absent in sham-treated dogs and in two dogs in which liquid nitrogen failed to produce obvious cortical lesions and the increase in brain water content caused by the lesion itself. Previously observed discrepancies between CSFP and CBF responses to different vasodilator agents allow to conclude that: (a) changes in CSFP depend not only on reactions of cerebral resistance vessels (which affect principally CBF and IVP) but also on reactions of cerebral capacitance vessels (which influence intracranial blood content only); and (b) cerebral resistance and capacitance vessels do not display the same patterns of reactivity to different pharmacological agents. Therefore, the present results indicate that there is a strict correlation between the acute brain lesion and the increased reactivity of brain capacitance vessels to Hi. In addition, the important position of Hi among autacoids suggests that this increased reactivity may represent an important step in a vicious circle involving local lesion, cerebral edema and intracranial hypertension.

SUMMARY: A. Waltz

**Session IV: Focal Lesions II**

**CHAIRMAN:** L. SYMON

**CO-CHAIRMAN:** J. HALSEY

**IV-22**

**False Autoregulation After Cold Injury to the Cerebral Cortex**—Miller JD, Garibi J, North JB, Teasdale GM (University Department of Neurosurgery, Institute of Neurological Sciences, Glasgow)

An increase in cerebrovascular resistance (CVR) with rising cerebral perfusion pressure (CPP) constitutes the normal physiological response of autoregulation (AR). This response may be present (in association with low CBF) in patients with severe brain damage, however, when AR is already impaired and, under these circumstances, increasing CVR has been termed "false autoregulation."

In the present study, the AR response to induced arterial hypertension was examined in the early stages of cerebral cold injury in eight anesthetized, ventilated baboons. CBF was measured in the affected hemisphere by 133Xe washout, ICP was measured from one or both lateral ventricles, and mean arterial pressure (MAP) was increased by intra-aortic infusion of norepinephrine. CPP was defined as MAP-ICP. After a control test of AR, cerebral cold injury was produced by liquid nitrogen. CBF was measured 30 and 60 minutes later, and then one or two further tests of AR were made.

Overall, the results indicated that, despite a smaller increase in CPP in the AR test after brain injury (due to lower MAP and a greater increase in ICP), there was a greater rise in CVR; this suggests that false autoregulation was present in the early stages of cerebral cold injury, at a time when brain edema was of very limited extent (as judged by Evan’s blue staining). This was most striking in three baboons in which AR was judged to be impaired during the control test. The CBF results in table 1 refer to mean (H/A) flow. The changes in fast component flow were more pronounced; thus, before the cold lesion, F_s increased by 52% during arterial hypertension, but only by 22% after the lesion. Also, the weight of the fast component decreased after the lesion, from 52% to 42%. In three baboons with a bilateral ventricular pressure recording, no significant pressure difference was observed when the recording was of satisfactory quality.

(The study was supported by the Secretary of State for Scotland’s Fund for Medical Research.)

**IV-23**

**rCBF and Regional Energy Metabolism in Cold Injury Edema as Affected by Moderate and Severe Hypocapnia and Hypercapnia**—Wallenfang Th, Schubert R, Reulen HJ, Schürmann K (Department of Neurosurgery, University of Mainz, Mainz, West Germany, Langenbeckstr. 1)

The present experiments were performed to study the influence of different arterial \( P_{CO_2} \) on \( rCBF \), energy-rich phosphate, lactate/pyruvate ratio as well as the water content of brain tissue in cerebral edema.

Brain edema was produced by a local cold injury under pentobarbital anesthesia in 40 cats. Twenty-four hours later \( rCBF \) was measured using \( ^{18}K \)Kr over (a) the lesion, (b) the perifocal edematous area, (c) a remote area, and (d) the contralateral hemisphere. Measurements were performed following: (1) normocapnia (\( M P_{CO_2} \) 29 mm Hg), (2) moderate hypocapnia (\( M P_{CO_2} \) 1.50 mm Hg), and (3) severe hypocapnia (\( M P_{CO_2} \) 1.17 mm Hg).

### Table 1 (IV-22)

**Mean Values of Eight Experiments**

<table>
<thead>
<tr>
<th>( P_{CO_2} ) mm Hg</th>
<th>Control</th>
<th>AR test</th>
<th>After cerebral cold injury</th>
<th>AR test</th>
</tr>
</thead>
<tbody>
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<td>40</td>
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<td>41</td>
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<td>60</td>
<td>88</td>
<td>54</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>1.33 gm/min</td>
<td>1.49</td>
<td>1.17</td>
<td>1.50</td>
<td>1.46</td>
</tr>
</tbody>
</table>

**CVR units**
SYMPOSIUM ABSTRACTS

PA\textsubscript{CO\textsubscript{2}} 16 mm Hg, (3) pronounced hypocapnia (M PA\textsubscript{CO\textsubscript{2}} 11.5 mm Hg), and (4) hypercapnia (M PA\textsubscript{CO\textsubscript{2}} 76.5 mm Hg). Following the above measurements the brain was frozen with liquid nitrogen. Water and metabolite contents were determined in areas in which CBF was measured.

Animals maintained in normoxic normocapnia showed a marked reduction of rCBF and a marked increase of lactate in the lesion and the adjacent area as compared to the control area. Under moderate hypocapnia rCBF increased significantly in the lesion as well as in the adjacent and remote area. CrP, ATP and water content showed a tendency to normalization in comparison to normocapnic conditions. Pronounced hypocapnia had an unfavorable effect upon brain edema and rCBF. Blood flow was lowered in all areas and brain water content was increased in the lesion and the adjacent tissue. Although ATP values differed not from normocapnic values, CrP was significantly reduced. Brain lactate and L/P ratio increased parallel to the decrease in PA\textsubscript{CO\textsubscript{2}} and fell with an increase in PA\textsubscript{CO\textsubscript{2}}.

During hypercapnia rCBF, edema and energy-rich phosphates showed no significant changes in the damaged hemisphere. In the uninjured hemisphere the well-known CO\textsubscript{2} response was observed only in four of ten animals.

The results show that the beneficial effect of hyperventilation on damaged brain may be obtained only with moderate hypocapnia. The shift of rCBF only with the healthy toward the diseased brain areas and the resolution of edema does not occur if the PA\textsubscript{CO\textsubscript{2}} is reduced more than 15 mm Hg.

IV-24 Quantitative Studies of Experimental Cerebral Edema—Dick A, Maxwell J, Nelson S (University of Kansas Medical School, Kansas City, Kansas)

There is a clear need for quantitative studies of the evolution of experimental cerebral edema and the effects of treatment modalities. There has been wide variation in edema models, measurement of edema, and treatment modalities. What, if any, CBF changes occur in quantitatively measured brain edema is largely unknown.

The present study was done with adult cats, paralyzed and artificially ventilated with 70% NO\textsubscript{2}, 30% O\textsubscript{2}, and 0.5% halothane. PA\textsubscript{CO\textsubscript{2}}, PA\textsubscript{O\textsubscript{2}}, arterial pH and MABP were monitored, and a steady state realized before edema or CBF determinations were made. Animals studied beyond six hours were allowed to awaken from anesthesia and were later reanesthetized.

Cold injury edema was created by dural application, through a trephine opening, of a liquid nitrogen-chilled copper probe. CBF measurements were made three, six and 24 hours after the lesion, by the C\textsuperscript{14} antipyrine method. Cerebral edema was quantitatively measured at 30 minutes, three hours, six hours, 15 hours, and 24 hours postlesion, using a method based on changes in specific gravity of brain when water content increases or decreases. A duplicate series of cats was given Decadron, 0.3 mg per kilogram per hour intravenously.

In the cortex, a 9% increase and, at 24 hours, a 10% increase in water content was seen. The subgyral white matter showed a 25% increase at three hours, and 30% at 24 hours. Deep white matter showed an increase in water content of 16% at three hours, 21% at six hours, and 22% at 24 hours. Decadron, given hourly, had no statistically significant effect on these values. CBF changes were largely confined to the white matter of the lesion hemisphere. A decrease in flow of 28% was seen at three hours, 32% at six hours, and 13% at 24 hours. CBF was not measured in animals receiving Decadron.

A rapid, simple and highly quantitative method of measuring cerebral edema has been employed to study the evolution of cold injury edema up to 24 hours. Although edema continues to spread, vertically more than horizontally in the hemisphere, it reaches maximal intensity within the first three hours. Decreases in CBF are most pronounced in the hemisphere white matter, and are maximal by three hours.

IV-25 Abstract has been withdrawn.

IV-26 Focal Autoregulatory Disturbances in Middle Cerebral Artery Vasospasm—Fein JM (Division of Neurosciences, Armed Forces Radiobiology Research Institute, Department of Neurosurgery, National Naval Medical Center, Bethesda, Maryland 20014)

The hemodynamic changes provoked by cerebral vasospasm are largely unknown. This study was designed to assess the influence of middle cerebral artery vasospasm on cerebral blood flow, autoregulation and responsiveness to arterial P\textsubscript{CO\textsubscript{2}} changes in the Rhesus monkey.

Spasm was induced by puncturing the middle cerebral artery, and the washout of \textsuperscript{133}Xe utilized to determine the “local” cerebral blood flow (CBF\textsubscript{l}) of the ipsilateral and contralateral middle cerebral, as well as the midline pericallosal, distributions. Initially (CBF\textsubscript{l}) varied inversely with the severity of spasm; however, the onset of infarction was marked by permanent depression of (CBF\textsubscript{l}) despite recovery of arterial caliber. In the face of wide changes in blood pressure, constancy of (CBF\textsubscript{l}) was present in the normal Rhesus monkey, and soon after the onset of spasm autoregulation of local middle cerebral blood flow was maintained during oligemic hypotension (55 to 75 mm Hg MBP), but flow values increased significantly during hypertension. Reflex vasodilatation and constriction could not be substantiated on serial angiography but changes in cerebrovascular resistances imply that the smaller (< 200 \mu) arterioles are still capable of dilatation. When prolonged (> 22 hours) spasm caused ischemic infarction, a reversal of the autoregulatory pattern occurred. In the latter group of animals autoregulation of (CBF\textsubscript{l}) was present during hypertension but (CBF\textsubscript{l}) values decreased markedly during modest hypotension. Despite autoregulatory disturbances in the midline pericallosal and contralateral middle cerebral distributions blood flow was maintained during normotension. Hypercarbia produced no alteration in flow during early spasm but evidence of an intracerebral “steal” was present in two of eight monkeys with...
The experimental production of miliary microaneurysms of small-sized arteries of the brain and of the iris of hypertensive albino rabbits has been demonstrated in our laboratories recently. The hypertensive state was induced by the production of unilateral silk-and-turpentine perinephritis followed by contralateral nephrectomy according to methods described by us previously. The morphological similarity between the arterial lesions in the brain and in the iris is thought to be related to the common embryological origin of both structures and also to the morphological similarities between the perforating arteries of the brain and the circular artery of the iris. The developing irido-arteriopathy in the presence of rising levels of blood pressure was followed photographically and by direct observation with an ophthalmoscope. Two types of hypertensive arteriopathy were detected in the iris: (a) 0 to 2+ changes which showed increased diameter and tortuosity of the circular artery and are probably reversible, and (b) 3+ to 4+ changes which demonstrate capillary hemorrhages and focal miliary microaneurysms formation in the circular artery and are irreversible. Histological study of the miliary microaneurysms detected in the brain and iris of these hypertensive rabbits has shown pathognomonic signs of Charcot-Bouchard arterial lesions, namely: focal, irregularly fusiform-shaped microaneurysms with “cellular disarrangement” or “fibrinoid” changes which contain lipid, and which may or may not have a mild inflammatory response. Miliary microaneurysms of the iris developed rapidly and in some cases these arterial lesions have been observed to develop fully within 48 hours in hypertensive rabbits. Characteristically, the irido-arteriopathy developed during the rising phase of the experimentally induced hypertension and appeared to clinically worsen when peak levels of blood pressure were reached. Ten percent to 15% of the hypertensive rabbits developed cerebral hemorrhages and invariably all of these hypertensive rabbits with cerebral hemorrhages have shown concurrence of 3 to 4+ irido-arteriopathy during life and cerebral arterial lesions at autopsy. (Supported by USPHS Grant HL 12521.)

RESERVE

A Comparison of Hypocapnia With Increased Volume Hyperventilation or Constant Volume Hyperventilation on CBF, CSFP, CMRO, and Cardiac Output One Day After Local Cold Injury to the Brain—Schutz H, Stoyka WW (Toronto 130, Ontario, Canada)

Ten dogs were anesthetized with nembutal 5 to 10 mg per kilogram. The trachea was intubated and the respiration was unassisted. A 1.5-cm burr hole was made and a copper tube applied to the exposed dura. The copper tube was kept filled with liquid nitrogen for five minutes. The animals were allowed to recover overnight and returned the following day. Animals were induced with thiopentone 5 to 10 mg per kilogram, intubated and ventilated. Anesthesia was maintained with Ketamine 5 mg per kilogram. The systemic arterial pressure (SAP), CSF pressure from the cisterna magna, extradural pressure (EDP) from the burr hole, end tidal CO₂, and thermal dilution cardiac output were monitored. Arterial and venous torcular FIP, FO₂, and


**SYMPOSIUM ABSTRACTS**

pH were measured. Hemoglobin and oxygen saturation were obtained with a co-oximeter and the CMRO₂ was calculated. Prior to the second procedure all animals had minimal neurological deficits (minimal hemiparesis). However, brain biopsy showed a hemorrhagic necrotic core with considerable white matter edema when the animals were sacrificed. Control values for ten dogs at a P<sub>10</sub> of 35 to 40 mm Hg were: CBF 32.7 ± 4.9 ml/100 gm per minute, CSFP 11.6 ± 2.8 mm Hg, CMRO₂ 2.6 ± 0.25 ml/100 gm per minute, and the cardiac output 166.0 ml per kilogram per minute. These values were significantly different from those obtained with normal dogs (P < 0.005). Autoregulation to changes in SAP was intact in seven of ten animals. Hypocapnia was produced by two methods using either increased respiratory rate or volume (increased volume hyperventilation) or constant volume hyperventilation with incremental removal of mechanical dead space. No significant difference was seen with these two techniques in the rate of decrease in cerebral blood flow to P<sub>10</sub> values of 10 to 15 mm Hg. However, CBF was shown to decrease at the rate of 0.6% CBF per mm Hg change in P<sub>10</sub>, compared to a value of 1.7% in normal dogs. With both types of hypocapnia CSFP increased to 19.0 ± 3.8 mm Hg. CMRO₂ and AVD O₂ remained constant. The cardiac output was 132.5 ml per kilogram per minute. Even with low P<sub>10</sub> values below 15 mm Hg there was no significant change in CBF and CMRO₂. It is concluded that hypocapnia induced by increased volume hyperventilation or by constant volume hyperventilation is similar in all respects in animals measured 24 hours following the ischemic cold lesions to the brain. Autoregulation was maintained in seven of ten animals but the CBF response to CO₂ was significantly reduced compared to normal animals.

**SUMMARY:** L. Symon

**Session V: Methodology I**

**THURSDAY (8:30 TO 10:45 A.M.)**

**CHAIRMAN:** N. LASSEN

**CO-CHAIRMAN:** W. OLDENDORF

**V-29**

Discrepancies in the Results of Flow Measurements Using Different Isotopes: 85-Krypton, 133-Xenon and 14-C-Antipyrine—de Valois JC, de Groot P (Dutch Central Institute for Brain Research, IJdijk 28, Amsterdam, The Netherlands)

In a series of nine rabbits a comparison was made between the usefulness of three isotopes to estimate the cerebral blood flow. Two inert gases, 85-Krypton and 133-Xenon, both dissolved in saline, and 14-C-antipyrine were used in this study. With the two inert gases the CBF was measured using the intra-arterial technique and recording of the gamma clearance over the intact skull. With 14-C-antipyrine the technique of Reivich as modified by Eklöf was used. This implies the sampling of arterial blood during an intravenous infusion of the isotope, at regular time intervals of five seconds. At the end of the infusion (after one minute) cardiac arrest is induced promptly by intravenous KCl.

The content of 14-C-antipyrine in the arterial samples and in the dissected brain areas is determined by liquid scintillation counting. From these data CBF can be calculated. By taking samples from homogenates of one hemisphere a value for the "mean" CBF can be obtained. In each animal CBF was measured consecutively with each isotope. The sequence of Krypton and Xenon was randomized. All measurements were completed within one hour after the start of the first CBF measurement. In this period the condition of the animal did not change significantly as judged from EEG readings, cardiac rate or P<sub>Co₂</sub> recordings.

The flow values obtained with 85-Krypton were considerably lower than with 133-Xenon:

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Gray Matter Flow (ml/100 gm per minute ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85-Kr</td>
<td>99 ± 11</td>
</tr>
<tr>
<td>133-Xe</td>
<td>129 ± 18</td>
</tr>
</tbody>
</table>

The relative weights of the gray matter were different, also: 34 ± 5% and 76 ± 9% for Krypton and Xenon, respectively. Unfortunately the data for the 14-C-antipyrine measurements were not available yet. They will be discussed in relation to the discrepancies mentioned above.

**V-30**

The Influence of Capillary Permeability Limitations on the Measurement of Regional Cerebral Blood Flow—Eckman WW, Phair RD, Fenstermacher JD, Sokoloff L (National Cancer Institute and the National Institute of Mental Health, Bethesda, Maryland 20014)

Theoretical and experimental studies have been combined to evaluate the role of capillary permeability in the measurement of regional cerebral blood flow by the autoradiographical diffusible indicator technique. Mathematical expressions developed by Kety (1951) were used to calculate blood flow from the tissue uptake of an inert diffusible substance. For the theoretical analyses, tissue uptake data were generated with a digital computer; a compartmental model was used to simulate the kinetics of exchange between capillary blood and tissue. Data were generated for a systematically varied range of blood flow and capillary permeability values, and the calculated flow rates were compared to the true blood flow values used in the simulations. In the experimental study, ¹⁴C-antipyrine uptake into the brains of normal unanesthetized cats was measured, and calculated regional flow rates were compared to blood flows previously measured by the uptake of an inert diffusible gas, CF<sub>4</sub>.

Both the theoretical and experimental analyses describe the extent of the errors in calculated blood flow which may result from a lack of equilibration between capillary blood and tissue. The errors are greatest for high rates of blood flow (F) and low permeability coefficient-surface area products (PS). Calculated flow is as low as 28% of the true flow for an F value of 1.8 cm<sup>3</sup> min<sup>-1</sup> gm<sup>-1</sup> and a PS value of 0.010 cm² sec<sup>-1</sup> gm<sup>-1</sup>. Calculated flow approaches 95% of true flow when PS is 0.012 cm² sec<sup>-1</sup> gm<sup>-1</sup> at an F of 0.1 cm³.
The experimental study demonstrated that 14C-nicotine uptake into cat brain is limited by both blood flow and capillary permeability. Regional blood flows measured with 14C-antipyrine were as low as 33% of those measured with the diffusible gas. PS values were calculated from these data, and comparison was made between the analytical and experimental studies. When the errors in calculated flow were plotted against PS values for various ranges of blood flow, there was found to be excellent agreement between the theoretically derived and experimental data. It is evident that capillary permeability limitations of 14C-antipyrine entry into brain may lead to considerable error in the measurement of regional cerebral blood flow. Because the magnitude of these errors is flow-dependent, there is hazard in using 14C-antipyrine for the measurement of regional cerebral flow in conditions where altered flow is being evaluated.

V-31

Brain Concentrations of 14C-Nicotine and 14C-Antipyrine After Intravenous Injection—Oldendorf WH (Wadsworth Hospital [691/151N], Veterans Administration, Los Angeles, California 90073)

A number of workers have measured regional blood flow in animals by injecting 14C-antipyrine intravenously and removing the brain about a minute later and carrying out autoradiography on coronal sections. The regional exposure is approximately proportional to regional blood flow. Antipyrine is suitable for this purpose because it is lipid soluble and nonvolatile; thus when it enters the microcirculation it diffuses through the brain endothelial capillary cell wall and distributes to a space which is considerably larger than the blood space in brain. Therefore, it behaves somewhat like multiple microemboli with the exception that it does not become unicompartmental, and furthermore hydrogen gas seems to be dysequilibrated between blood and tissue making for shorter autoradiography exposure time. The subsequent brain concentrations of nicotine were more constant than antipyrine. This more constant brain concentration makes the time of study less critical. If nicotine were to be substituted for antipyrine in such experimental studies it would be necessary to be certain that the actual amount of nicotine injected would not produce a significant vascular response on a pharmacological basis. It is possible that C-11 nicotine could be produced biologically from tobacco leaf and used in human studies using external measurement of regional blood flow.

V-32

Variation in Gamma Index (Dimensionless Dispersion) of Hydrogen Gas in a Single Human Brain—Tomita M, Gotoh F (Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan)

The dimensionless dispersion, i.e., standard deviation of distribution function divided by mean transit time, is a generalized measure of multiplicity of pathways of indicator. Therefore, it may provide a rough estimate of the character of channels through a “black box.” As for the circulatory system the value of 0.18 has been reported by Bassingthwaighte in a peripheral artery (a tubular channel) where blood flows with a certain velocity profile, 0.28 in the heart aorta system (a saccular channel) where turbulence or eddies are occurring in the blood stream, and 0.46 in the pulmonary vascular bed (multiple channels) studied with nondiffusible substances. The value of 1 suggests that the channels make up a perfect mixing chamber or a first order compartment, and values more than 1 multiple compartments arranged in parallel. Because of the conceptual importance this sense of dimensionless dispersion has been named by us gamma index after its close relation to gamma variance.

To investigate variation of gamma index in a single human brain, five pairs of cerebral arteriovenous desaturation curves of hydrogen gas, which had been obtained from a volunteer subjected to various procedures successively, were deconvoluted by the modified Neufeld method using Z transform. From the resultant distribution functions computed were the values of gamma index; 1.1 in the control state, 0.95 during 5% CO2 inhalation, 0.7 during 10% CO2 inhalation, 1.1 after aminophylline injection, and 1.2 after amytal injection. These data show that the brain is usually multicompartmental with respect to blood flow. But, with 5% CO2 inhalation the same brain seems to become unicompartmental, and furthermore hydrogen gas seems to be dysequilibrated between blood and tissue as blood flow is increased tremendously by 10% CO2 inhalation. It is speculated that flow compartments in a brain estimated from desaturation curves of diffusible substances are of functional origin rather than organic.

SYMPOSIUM ABSTRACTS

Min-1 gm-1, whereas a PS of 0.120 cm3 sec-1 gm-1 is necessary for a flow rate of 1.8 cm3 min-1 gm-1 in order to achieve the 95% level of accuracy.

The regional exposure is approximately proportional to regional blood flow. Antipyrine is suitable for this purpose because it is lipid soluble and nonvolatile; thus when it enters the microcirculation it diffuses through the brain endothelial capillary cell wall and distributes to a space which is considerably larger than the blood space in brain. Therefore, it behaves somewhat like multiple microemboli with the exception that it does not become unicompartmental, and furthermore hydrogen gas seems to be dysequilibrated between blood and tissue making for shorter autoradiography exposure time. The subsequent brain concentrations of nicotine were more constant than antipyrine. This more constant brain concentration makes the time of study less critical. If nicotine were to be substituted for antipyrine in such experimental studies it would be necessary to be certain that the actual amount of nicotine injected would not produce a significant vascular response on a pharmacological basis. It is possible that C-11 nicotine could be produced biologically from tobacco leaf and used in human studies using external measurement of regional blood flow.

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SYMPOSIUM ABSTRACTS

V-33
Determination of Diffusion Shunt in Brain and Its Influence on Blood Flow Measurements. A Diffusion Shunt Model—Lübbers DW, Wodick R. (Max-Planck-Institut für Arbeitsphysiologie, Dortmund, Germany)

Diffusion shunt in the brain was detected for hydrogen by Stoszec and for Xenon by Brodersen, Segresen and Lassen. The development of a generally valid model permitted us to derive mathematical expressions for diffusion shunts in brain. With clearance measurements under very general conditions, we could prove that after slow saturation with an indicator gas and following evaluation according to Ingvar and Lassen, as well as with "slug" injection and following evaluation according to Zierler, one obtained a flow value reduced by the factor (1-s). s means the shunt parameter and indicates the probability that an indicator particle flows through the shunt, and not through the supply area.

From clearance measurements with two indicators having different diffusion constants D1 and D2, it was possible to determine the true blood flow value b as:

\[ b = b_1 + \frac{b_1 b_2}{D_1 (1 + \frac{b_1 - b_2}{b_1})} \]

b1 and b2 are the apparent blood flow values measured with the two indicators and evaluated, for example, according to Ingvar and Lassen or to Zierler. The shunt parameters s1 and s2 were determined for the two indicators as:

\[ s_1 = \frac{b_1 - b_2}{b_2 (D_2 - 1)} \quad \text{and} \quad s_2 = \frac{b_2 - b_1}{b_1 (D_1 - 1)} \]

By computing the relation of the value s and the diffusion constant D to the mean time of presence of an indicator molecule in the shunt area, we found for the shunt parameter that:

\[ s = \frac{A \tilde{t}_D}{1 + (1 + 1/n) A \tilde{t}_D} \quad \text{with} \quad n = \frac{b_1 \tilde{t}_D}{b_2 \tilde{t}_D} \]

\( \tilde{t} \) is in inverse proportion to the mean blood flow velocity divided by shunt.

The above formulas permitted us to evaluate the true blood flow and the shunt.

V-34
Heterogeneity of Regional Cerebral Blood Flow and Regional Distribution of Relative Weights of Gray and White Matter in Normal Subjects—Herrschaft H, Gleim F, Duus P, Schmidt H (Departments of Neurology and Anesthesiology, Akademisches Krankenhaus Nordwest der Johann-Wolfgang-Goethe-Universität, Frankfurt [Main], Germany)

Normal values of regional cerebral blood flow were estimated in 22 healthy volunteers, using the intra-arterial 133Xenon clearance method and the multidetector equipment of Siemens. The equipment guarantees: (1) non-overlapping measurement in ten areas evenly distributed over a cerebral hemisphere, (2) accurate assignment of local cerebral blood flow readings to the cylindrically shaped measurement spaces within a cerebral hemisphere, the size, position and blood supply of which are precisely determinable.

In order to exclude psychic factors and to maintain a steady state over a period of 30 minutes (double experiments), the examinations were carried out in flat nitrous oxide-halothane analgesia. rCBF values were calculated by a computer program which, by compartmental analysis, delivers regional values for perfusion of gray matter (Fg), perfusion of white matter (Fw), the relative weight of gray matter in the measurement area (Wg) and the weighted mean flow value for the region (F). Moreover, the program gives the regional average CBF for a period of ten minutes and to infinity by the stochastic analysis (Finf, Fco).

The results were: (1) Total average flow values (ml/100 gm per minute): Fg = 106.5, SE 20.6; Fw = 24.4, SE 4.5; Fco = 63.1, SE 12.9; Fstock = 56.5, SE 11.5. (PaO2 = 40.0, PaCO2 = 113.2, MABP = 100.7 mm Hg.)

(2) Normal values of regional cerebral blood flow varied considerably in the 22 persons, whereas the intra-individual rCBF changes of repeated tests at an interval of 15 minutes turned out to be very low (<±5%).

(3) Interregional differences in CBF and in the distribution of gray and white matter were found which achieved statistical significance.

(4) The perfusion of gray matter (Fg) was high in the precentral and central regions and in the region of basal ganglia, and low in the frontal and occipital regions.

The regional weighted mean flow values (F) and the regional CBF values (Fco, Fstock) yielded on principle the same type of distribution.

(5) The perfusion of white matter (Fw) was rather uniform. Only in the frontobasal region was it less perfused than elsewhere in the hemisphere.

(6) The regional distribution of the gray matter was well shown by this method, with high values in the region of basal ganglia (55%), low values over the corpus callosum and corona radiata (44% to 46%) and intermediate values in the rest of the regions (50% to 52%).

V-35

Previous work from this center has shown by correlating two-compartmental analysis of isotope clearance curves with anatomical dissection that in normal brain has not been studied. More recently of gray and white matter corresponded to the true anatomical proportions. The situation at hypocapnia in normal brain has not been studied. More recently evidence has accumulated to suggest that in pathological states the distinction between gray and white matter cannot be made so readily. We have carried out a study to see whether the ratio of Wg/Ww remains constant in the same area at different flow values.
Using intra-arterial injection of $^{133}$Xenon, measurements of cerebral blood flow were made in 15 regions in patients with ischemic cerebrovascular disease. The group consisted of eight males and four females, whose average age was 49. All patients were studied under general anesthesia; 15-minute clearance curves were obtained at normocapnia and then hypocapnia. The mean $P_{\text{CO}_2}$ of the normocapnic study was 42 mm Hg and there was a fall of between 12 and 23 mm Hg with hyperventilation. The table summarizes the results. Hypocapnia caused a fall in blood flow which was consistently accompanied by a relative decrease in $W_g$. Regional changes were not significantly different from the means. There was a significant negative correlation between the percent changes in $F_g$ and $W_g$ in ten areas out of 15, suggesting that large changes in flow were most often associated with relatively small changes in weight and vice versa.

Our conclusions are that under pathological conditions, $W_g$, as determined by isotope clearance, is an imprecise measurement of the proportionate weight of gray matter and that $F_g$ and $F_w$ are misnomers and might more appropriately be renamed Flow fast ($F_f$) and Flow slow ($F_s$).

**V-36**
Regional Cerebral Blood Flow—Evaluation of the Microsphere Technique—Shulman K (Department of Neurosurgery, 1300 Morris Park Avenue, Bronx, New York 10461), Furman M, Rosende R

The use of radioactive microspheres to measure regional blood flow is based upon the principle that the distribution of the spheres is proportional to flow if removed by the organ studied in the first transit, and if the spheres are completely mixed in the blood entering the organ. For the brain, since the $15 \pm 5 \mu$ spheres occlude capillaries, one must also demonstrate that such occlusions do not cause tissue hypoxia. The experiments reported in this paper were designed to answer two questions: (1) Are $15 \pm 5 \mu$ microspheres completely removed during their first transit through the cat brain? and (2) Is there subsequent tissue anoxia? Approximately 400,000 spheres were introduced into the left atrium via a thoracotomy and multiple small areas of the brain sampled after sacrifice for count rates. Sagittal sinus or jugular venous blood was sampled and demonstrated no appreciable number of counts. Brain lactate and pyruvate in control animals were 3.2 and 0.13 $\mu$ moles per gram net weight of tissue with an L/P ratio of 24.6. In the animals receiving the microspheres, brain lactate was 3.4 $\mu$ moles and pyruvate 0.12 $\mu$ mole per gram net tissue weight with an L/P ratio of 26. We conclude that $15 \pm 5 \mu$ microspheres satisfy the criteria of a useful agent for study of regional flow differences and areas of nonhomogenous flow in the experimental animal.

**V-37**
Pulsatile Blood Flow Pattern in Cerebral Circulation—Nornes H (Neurosurgical Department, University Hospitals, Rikshospitalet, Oslo, Norway)

Electromagnetic blood flowmetry (EMBF) has certain advantages compared with other methods. It allows a continuous registration of mean BF in a defined vascular system. In addition, the instantaneous or pulsatile BF can be recorded. Few have tried to analyze this parameter which also contains information on the condition of runoff.

In ten patients protracted bilateral EMBF on the internal carotids arteries (ICA) was made during graded occlusion for a saccular aneurysm. When the ICA flow was reduced to about 50% to 60% of control by means of a Silverson clamp, the pulsatile amplitude showed approximately the same relative reduction as the mean BF. If, however, the mean ICA flow was reduced to the same degree by hypocapnia (voluntary hyperventilation), the pulsatile amplitude remained unchanged or even increased. A detailed study of the whole pulsatile complex showed, however, certain changes in the flow profile.

### TABLE (V-35)

<table>
<thead>
<tr>
<th>Area no.</th>
<th>No. of measurements</th>
<th>Mean % fall in $F_g$</th>
<th>Mean % fall in $F_w$</th>
<th>Mean % fall in $W_g$</th>
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<td>11</td>
<td>47.6</td>
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<td>7</td>
<td>36.1</td>
<td>33.6</td>
<td>37.8</td>
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</tbody>
</table>

Mean and SE: 51.4 (4.1), 44.0 (3.0), 18.8 (3.5)

Stroke, Vol. 4, May-June 1973
The explanation for these observations is that a change in resistance to flow is nearly the same in both situations, but the impedance to flow is different. With the measuring probe in the same position this difference is determined by the site of the main resistance-impedance change, and also implies possible changes in the arterial system (vessel compliance) between the probe and this site.

The second part of the study was conducted on nine patients with miniature EM flow probes on cerebral vessels during surgical procedures for carotid-cavernous fistulas, saccular aneurysms, and A-V malformations.

An arterial blood flow reaching an arterial network through a collateral pathway such as the circle of Willis may have a different phasic flow compared with that supplied by the genuine arterial channel. The pulsatile pattern and the mean BF are both of considerable importance for the understanding of the hemodynamic state and for the determination of tolerance to temporary or permanent vessel occlusions.

RESERVE

**Heterogeneity of Tritiated Water Uptake by the Brain**

Moran JH, Klassen AC, Meyer MW (Departments of Neurology and Physiology, University of Minnesota, Minneapolis, Minnesota 55455)

Various radioactive diffusible indicators have been used to study regional distribution of brain blood flow. Recent studies by others have suggested that the use of labeled iodoantipyrine as a diffusible indicator may be misleading. Although with tritiated water (THO) some counter-current exchange may occur, THO may still provide additional evidence about regional differences in brain blood flow. THO was administered by constant infusion via the left atrium of 13 open-chested anesthetized dogs. About 30 seconds after beginning infusion the aorta was incised. The brain was removed, taking about ten minutes, and placed in liquid nitrogen. Samples were taken from various regions and dissolved, and activity was determined using liquid scintillation counting techniques. From other samples, the fraction of water content was determined and the activity per gram of water (A) in various tissues calculated. It was impractical to sample the entire brain to obtain an average activity value (A). Instead, average A in gray (g) and white (w) tissues was calculated for each animal and an A determined (A = 0.6 A_g + 0.4 A_w). Heterogeneity of THO uptake was then described as the ratio of A in each tissue to A. The average (A/A) values for the various tissues were: cerebellar cortex, 1.02 ± 0.07 (SE); cerebellar white, 0.79 ± 0.06; pons, 0.92 ± 0.04; midbrain, 1.03 ± 0.06; cerebral cortex, 1.20 ± 0.05; cerebral white, 0.68 ± 0.04; thalamus, 1.22 ± 0.06; caudate, 1.33 ± 0.05; hypothalamus, 1.08 ± 0.04; and pituitary, 2.47 ± 0.28. This approach provides additional evidence about regional differences in brain blood flow. THO was administered by constant infusion via the left atrium of 13 open-chested anesthetized dogs. About 30 seconds after beginning infusion the aorta was incised. The brain was removed, taking about ten minutes, and placed in liquid nitrogen. Samples were taken from various regions and dissolved, and activity was determined using liquid scintillation counting techniques. From other samples, the fraction of water content was determined and the activity per gram of water (A) in various tissues calculated. It was impractical to sample the entire brain to obtain an average activity value (A). Instead, average A in gray (g) and white (w) tissues was calculated for each animal and an A determined (A = 0.6 A_g + 0.4 A_w). Heterogeneity of THO uptake was then described as the ratio of A in each tissue to A. The average (A/A) values for the various tissues were: cerebellar cortex, 1.02 ± 0.07 (SE); cerebellar white, 0.79 ± 0.06; pons, 0.92 ± 0.04; midbrain, 1.03 ± 0.06; cerebral cortex, 1.20 ± 0.05; cerebral white, 0.68 ± 0.04; thalamus, 1.22 ± 0.06; caudate, 1.33 ± 0.05; hypothalamus, 1.08 ± 0.04; and pituitary, 2.47 ± 0.28. This approach provides additional evidence about regional differences in brain blood flow. (Supported by NIH Grant No. NB 03364.)

**SUMMARY:** N. Lassen

**Session VI: Diffuse Ischemia I**

**THURSDAY (11:00 A.M. TO 12:45 P.M.)**

**CHAIRMAN:** B. Siesjö

**CO-CHAIRMAN:** J. Posner

**VI-38**

**Moderate Hypoxic Ischemia Irreversibly Damages Rat Brain in 30 Minutes**

Brierley JB, Salford LG, Siesjö BK, Plum F (MRC Neuropsychiatry Unit, Carshalton, England, Brain Research Laboratory, Eblen, University Hospital, Lund, Sweden, and Department of Neurology, Cornell Medical Center, New York, New York)

The purpose of the investigation was to decide whether pure hypoxemia can lead to irreversible neurophysiological and biochemical alterations in the brain or whether some additional oligemia is required. Using the Levine (one carotid artery ligated) preparation in the rat, arterial PaO_2 was reduced to 28 or 21 mm Hg and maintained there while blood pressure was kept at 120 mm Hg or more. Animals (half for morphological and half for biochemical studies) were killed after one-half hour of hypoxemia or after a further half hour of resuscitation (ligature removed and arterial oxygen tension normalized). For histological study, brains were saline-rinsed and perfusion-fixed with formalin, and stained for light microscopy. For studies of adenine nucleotides and carbohydrate intermediates the freezing technique of Siesjö was employed followed by fluorometric analysis.

Pure hypoxemia (nonligated hemispheres) produced no immediate or enduring morphological alterations. Biochemical abnormalities disappeared after 30 minutes' recovery.

At the end of exposure to hypoxic-ischemia (ligated hemispheres) morphological abnormalities were found in no PaO_2 (28) animals and in only one of nine PaO_2 (21) animals. However, after 30 minutes' recovery, some animals in both groups showed histological abnormalities which were moderate in four of seven PaO_2 (28) animals and more pronounced in seven of ten PaO_2 (21) animals. In contrast to the morphological changes, ATP had declined and L/P ratios were elevated in the ligated hemispheres of all animals at the end of the hypoxic-ischemic exposure, but residual chemical abnormalities persisted after 30 minutes' recovery only in the PaO_2 21 group.

Evidently moderate hypoxemia with additional slight relative ischemia of no more than 30 minutes' duration can result in irreversible neuronal alterations as detected by the light microscope. These findings are incompatible with current suggestions that the brain can tolerate prolonged and total ischemia without sustaining irreversible injury.

**VI-39**

**Disturbances of Cerebral Microcirculation After Cerebral Ischemia**

Matakas F, Fuchs E, Cuypers J (Klinikum Steglitz-der freien Universität, Berlin, West Germany)

In two groups of animals, both consisting of monkeys and cats, complete cerebral ischemia was produced for 25 minutes by clamping the brachiocephalic and subclavian arteries and simultaneous moderate arterial
hypotension (80 to 90 mm Hg). During the postsischemic period the EEG, ECG, arterial and venous blood pressure, intracranial pressure (epidural), CBF (in monkeys), body temperature, serum electrolytes, acid-base balance, and fluid balance were monitored as long as the animals could be kept alive (6 to 48 hours).

Group 1: The eight animals of this group were not subjected to any treatment. None of them recovered spontaneously. Within a few hours after ischemia they developed arterial hypotension while the intracranial pressure approached the arterial blood pressure. Later hypokalemia and polyuria were observed. CBF progressively diminished to zero. Light and electron microscopical examinations revealed the criteria of brain death. All cerebral capillaries showed damage and swelling of the endothelium and narrowing or obstruction of the capillary lumen. Group 2: In this group of 19 animals the blood pressure was artificially elevated to values between 140 and 180 mm Hg immediately after ischemia. Intracranial hypertension was only moderate. Electrical activity of the cortex and spontaneous breathing returned in 12 cases. Diuresis and serum electrolytes were unchanged. Fine structure analysis showed damage of neurons and glia but only minor lesions of capillaries. The animals showed morphological changes similar to those which may be observed in the apallic syndrome in man.

The experiments indicate that in cases of cerebral ischemia it is not only the immediate anoxic damage to neuronal or glial cells that determines the postsischemic development. Apart from postsischemic brain edema, which reduces the intracranial perfusion pressure, obstruction of capillaries produces a regional or total stop of the cerebral circulation. Moreover, the capillary lesions seem to develop further or to become irreversible after the ischemic period if the general hemodynamic conditions are not optimal. Luxury perfusion thus can be impaired in spite of vasoparalysis.

VI-40 
**Postsischemic Recovery of Nucleotide Metabolism in the Cat Brain**—Kobayashi K, Kleihues P, Hossmann K-A, Brown B (Max-Planck-Institut für Hirnforschung, Cologne, West Germany)

Purine nucleotide metabolism was investigated after one hour of complete ischemia, produced in anesthetized (Nembutal) cats by clamping of the innominate, the left subclavian and both internal mammary arteries combined with simultaneous lowering of the blood pressure. After recirculation, functional recovery was assessed by recording the EEG and the pyramidal response to electrical stimulation of the sensorimotor cortex. Acid-soluble nucleotides were separated by ion-exchange chromatography on DEAE-Sephadex columns. Nucleosides and free purine bases were analyzed on DOWEX 50 x 4 columns (NH\textsubscript{4}\textsuperscript{+} form).

After one hour of complete ischemia, there were no detectable amounts of ATP and the energy charge of the adenylate pool—(ATP + ADP)/(AMP + ADP + ATP)—was reduced from 0.83 to less than 0.05. In contrast to ATP, GTP was only catabolized to about 30% of the control range. The concentration of total adenine (AMP + ADP + ATP) and guanine (GMP + GDP + GTP) nucleotides was reduced to approximately 35% and 65% of control levels, respectively. There was a tenfold increase in nucleosides and free purine bases, the main products of catabolism being adenosine, inosine and hypoxanthine.

In animals with signs of functional recovery, ATP and total adenine nucleotides increased to about 60% of control levels during the initial six to eight hours of recirculation. At this time, the energy charge ratio had already returned to the normal range. GTP concentrations also increased but the sum of guanine nucleotides remained almost unchanged. Radiocromatographic studies in animals which, 60 minutes prior to death, received an intravenous injection of Na\textsuperscript{+}{[\textsuperscript{14}C]} formate indicate a marked enhancement of the de novo synthesis of purine nucleotides during the postsischemic recovery phase. The significance of re-utilization of purine nucleotides by salvage pathways will be discussed.

The data presented demonstrate that cerebral energy metabolism may recover after extended periods of complete ischemia if an efficient recirculation of the brain can be achieved.
SYMPOSIUM ABSTRACTS

Na+/K+ quotient rose to 0.78. CBF and brain water normalized within three hours, and the Na+/K+ quotient within 24 hours.

(3) Animals without functional recovery despite re-circulation (five experiments): After ischemia CBF was below normal and eventually ceased. Maximal water uptake was less than in the group with recovery, but the water content did not normalize and the Na+/K+ quotient gradually increased to 0.87 in the gray and to 0.74 in the white matter.

It is concluded that functional recovery after ischemia correlates well with the regression of brain swelling and electrolyte derangements; the limiting factor for recovery, however, appears to be the state of the blood flow and not the extent of swelling.

VI-42
Anoxia and Critical Oxygen Tension in Brain Tissue—Lübbers DW, Starlinger H (Max-Planck-Institut für Arbeitsphysiologie, Dortmund, Germany)

The development of a new technique allowed us to simultaneously register the redox state of the different members of the respiratory chain, and to polargraphically measure the oxygen tension under steady-state conditions in isolated mitochondria. Measurements in mitochondria of different organs, including brain, showed that the reduction of the respiratory chain is brought about at oxygen tensions below 0.05 to 0.1 torr. Similar results had been obtained before with measurements in liver mitochondria by a luminescence technique (Schindler and Chance). It is important to state that the generally used polargraphical methods are not sensitive enough to correctly measure such low oxygen tensions. Therefore, a polargraphically measured \( P_{O_2} \) of "zero" cannot be understood as a sign of local brain anoxia. Such a conclusion can be drawn only from a \( P_{O_2} \) histogram.

VI-43
The Effect of Ischemia and Hypoxia on the Pyridine Nucleotide Redox State of the Cerebral Cortex of Cats—Harbig K, Reivich M (University of Pennsylvania, Philadelphia, Pennsylvania)

In a series of 25 cats the PN redox state was measured with a compensated microfluorometer with a reflectance device to correct for hemodynamic artifacts. The animals were anesthetized with nembutal 40 mg per kilogram I.P. and paralyzed with flaxedyl 10 mg per kilogram I.V. Respiration was controlled and end tidal \( P_{VCO_2} \), blood pressure and EEG were continuously monitored. Arterial and cerebral venous blood samples were obtained for blood gas determinations. In seven animals cerebral perfusion was reduced by elevating intracranial pressure and in another nine by lowering arterial blood pressure by bleeding. In the former group a definite NADH increase occurred when the cerebral perfusion pressure (CPP) was reduced to 60 mm Hg and increased continuously to a maximum of 20% of full scale when CPP was reduced to zero. During the ensuing compression ischemia which was maintained for up to six minutes, the NADH increased further to a maximum of 40%. When CPP was increased again, even by only 5 mm Hg, reoxidation of NADH progressively increased and full recovery occurred at a CPP of 80 mm Hg. With bleeding a definite increase in NADH occurred at a CPP of 90 mm Hg and increased to a maximum of 25% at a CPP of 10 mm Hg. Full recovery produced by reinfusion of blood occurred at a CPP of 100 mm Hg. The EEG became isoelectric in the first group when the CPP was about 10 mm Hg and recovered when it was increased to 60 mm Hg. In the second group the electrical activity ceased when the CPP was about 20 mm Hg and recovered when it was about 50 mm Hg.

In ten animals hypoxia was produced by decreasing the inspired \( O_2 \) concentration in a stepwise manner. A definite NADH increase occurred at a \( P_{O_2} \) between 50 to 60 mm Hg. Cerebral venous \( P_{O_2} \) was 32 mm Hg at this time. \( P_{O_2} \) was reduced to a minimum value of 20 to 30 mm Hg at which time \( P_{O_2} \) was 16 mm Hg and NADH had increased to 25%. When \( P_{O_2} \) fell to < 30 mm Hg, EEG amplitude began to decrease and became isoelectric in some animals at \( P_{O_2} \) levels between 20 to 27 mm Hg. The EEG became isoelectric only in those animals whose blood pressure fell markedly.

VI-44
Cerebral Blood Flow and Metabolism at Different Levels of Decreased Cerebral Perfusion Pressure Induced by Reised Intracranial Pressure and Normovolemic Arterial Hypotension—Hamer J, Hoyer S, Stoeckel H, Alberti E (Departments of Neurosurgery and Anesthesiology, Institute of Neurochemistry, University of Heidelberg, Heidelberg, Germany)

In 20 anesthetized, artificially ventilated normocapnic mongrel dogs cerebral perfusion pressure (CPP) was decreased to values of 70 mm Hg (stage 1) and 40 mm Hg (stage 2). In group A (10 dogs) CPP was lowered by infusing mock CSF into the cisterna magna, keeping MABP at a constant level. In group B (10 dogs) CPP was decreased by injecting trimethaphan (Arfonad). After a steady state of 30 minutes the following measurements were carried out: (a) CBF, determined by the Kety-Schmidt technique (modified by Bernsmeier and Siemons), (b) the cerebral arteriovenous differences of oxygen, glucose and lactate, measured by gas chromatography, respectively enzymatically. Before and after each measurement, AVD-\( P_{O_2} \), \( P_{CO_2} \) and pH were controlled. Blood samples were taken from the femoral artery and the superior sagital sinus. MABP, CVP, SSP and CSFP were continuously recorded. Statistical calculations were based on the F test and t test.

Group A: CBF (mean value: 65.3 ml/100 gm min) decreased at a CPP of 70 mm Hg for about 22% (51.2 ml/100 gm min). At a CPP of 40 mm Hg, CBF fell to 29.8 ml/100 gm min (54%). \( AVD-O_2 \) was unchanged at a CPP of 70 mm Hg, but increased for about 18% at a CPP of 40 mm Hg. CMRO\(_2\), however, was diminished for 39% in stage 2. With falling CBF, AVD-glucose did not increase in a compensatory fashion. Thus, glucose consumption was significantly decreased at a CPP of 40 mm Hg. Cerebral output of lactate was markedly increased, even at a moderate decrease of CPP.

Group B: (mean value: 61.1 ml/100 gm min) was not altered at stage 1 (60.6 ml/100 gm min), but...
cells showed reactive changes as proliferated rough
decreased during this phase and lactate increased. In the
of glycolysis at different levels of decreased CPP will be
revealed no damage or disintegration of the endothelial
tended to slow waves.
animal died. In the second phase the EEG spectrum
and finally the ATP contents were diminished and the
beginning of the second phase ATP remained un-
Cr~P system as well as lactate and pyruvate in the tissue
CMR-glucose remained constant, compared to the
sagittal sinus and its correlation to cerebral hemody-
discussed in particular.
The different patterns of pressure changes within the sagittal sinus and its correlation to cerebral hemody-
namics will be shown.
RESERVE
The Significance of Cerebral Cortical Hypoxia in Experi-
mental Shock Induced by Endotoxin—Schmahl FW, Schlotte
W, Heuser D, Betz E (Institute of Physiology [I], De-
partment of Submicroscopic Pathology, University of Tuebingen and Department of Internal Medicine, Uni-
versity of Giessen, West Germany)
In cats, anesthetized initially with 25 mg per kilogram
pentobarbital, 1 mg per kilogram endotoxin was injected
intravenously. Local cortical blood flow was continuously
recorded with heat clearance devices and arterial P\textsubscript{o2}
with the Micro-Astrup technique. Cortical P\textsubscript{o2}
was measured with a multi-wire platinum electrode on
different spots of the cortical tissue. In some experi-
ments the course of local P\textsubscript{o2}
was measured continu-
ously during the whole experiment. At various times
after endotoxin injection small samples of cortical tissue
were excised by means of a steel punch cooled in liquid
nitrogen. The energy-rich phosphates of the ATP and
Cr~P system as well as lactate and pyruvate in the tissue
samples were determined with enzymatic methods.
During the first minutes after injection a sharp, but
transient decrease of arterial blood pressure was
recorded (early phase of endotoxin shock). rCBF and
cortical P\textsubscript{o2}
followed the course of blood pressure in
varying degrees, depending on whether autoregulation
was maintained or not. A secondary decrease of pressure and flow was observed several hours after
injection (late phase of endotoxin shock). Cortical P\textsubscript{o2}
decreased during this phase and lactate increased. In the
beginning of the second phase ATP remained un-
changed, Cr~P showed only slight decreases and the
EEG frequency spectrum was unchanged in the initial
phase. When rCBF decreased because of a reduction of
arterial blood pressure below a critical level the Cr~P
and finally the ATP contents were diminished and the
animal died. In the second phase the EEG spectrum
tended to slow waves.
Electron microscopic studies of the cortical tissue
revealed no damage or disintegration of the endothelial
cells' layer of cortical capillaries, but some endothelial
cells showed reactive changes as proliferated rough
endoplasmic reticulum and Golgi cisterns. (Supported
by the Deutsche Forschungsgemeinschaft, Be 324/11.)
SUMMARY: B. Siesjö
Session VII: Diffuse Ischemia II
THURSDAY (2:00 TO 3:45 P.M.)
CHAIRMAN: D. LUBBERS
CO-CHAIRMAN: J. BRIERLEY
VII-45 Tissue-P\textsubscript{o2}
and Cell Function in the Microarea of the Brain
During Hypoxia—Erdmann W, Kunke S (Departments
of Anesthesiology and Physiology, University of Mainz, Germany)
By means of a gold multimicroelectrode with seven
electrode tips of 1 to 5 μ in diameter arranged equidistant over an area of 50 μ a three-dimensional
registration of tissue-P\textsubscript{o2}
and action potentials is possible.
(1) Response of local tissue-P\textsubscript{o2}
and action potential rate to respiratory hypoxia has been studied in various
parts of the brain of albino rats.
When tissue-P\textsubscript{o2}
falls below a certain level, cell activity stops all of a sudden. This critical P\textsubscript{o2}
value is quite different for cells with high normal P\textsubscript{o2}
values and those with low ones. It ranges between 10 and 20 mm
Hg in the arterial part of the capillary mesh work and
below 0.5 mm Hg in the venous part.
During respiratory hypoxia cells in the venous part of
the capillary mesh work with low tissue-P\textsubscript{o2}
and low critical P\textsubscript{o2}
values do not suffer from hypoxia before
those in the arterial part. During respiratory hypoxia the
P\textsubscript{o2}
gradients in the intercapillary space become much
smaller as an effect of blood flow increase. Cell function
stops at inspiratory oxygen concentrations of about 10
vol %, at first in the arterial part of the capillary mesh
work.
(2) In a second series of experiments local tissue-P\textsubscript{o2}
and cell function have been studied during compression
of the arteria carotis.
During occlusion of the arteria carotis microcircula-
tion in the same side of the brain tissue is decreasing.
The gradient of tissue-P\textsubscript{o2}
becomes much higher as oxygen tension is only reduced in the venous part of the
capillary mesh work. When microcirculation is dimin-
ished by one-fourth of the normal value cell function
stops already at more than half of the registered points
in the tissue, thus revealing the important fact of
cerebral autoregulation.
VII-46 Intracranial Pressure, Brain Blood Flow Regulation and
Glucose and Oxygen Metabolism After 15 Minutes of
Circulatory Arrest in Dogs—Snyder J, Nemoto E, Carroll
R, Morita H, Safar P, Kirimli B (Department of Anes-
thesiology/CCM, University of Pittsburgh School of
Medicine and Oakland VA Hospital, Pittsburgh, Penn-
sylvania 15213)
The cause of brain hypoperfusion postischemia (PI)
is not known. Clinical observations indicate brain
swelling. Our previous studies on dogs showed a
SYMPOSIUM ABSTRACTS

moderate, transient rise in cisterna magna pressure (CMP) with no secondary rise for eight hours PI. In this study we measured subdural supracortical pressure (SCP) and CMP for indications of brain swelling and cerebral herniation.

Capillary pinch and RBC aggregation (i.e., mechanical obstruction) have been hypothesized to be the cause of PI brain hypoperfusion. Increase in cerebral perfusion pressure (CPP) has been reported to improve flow. We determined cerebrovascular reactivity to CO₂ and CPP in hypoperfused PI brain to test this hypothesis and to verify the effects of CPP on regional cerebral blood flow (rCBF).

We also measured relative changes in cerebral metabolic rate for glucose (CMRGl) and oxygen (CMRO₂) to assess PI cerebral metabolism.

Dogs initially anesthetized with I.V. Surital and paralyzed with gallamine (2 mg per kilogram) were kept at a Pa(O₂) of about 40 mm Hg with 50% N₂O/50% O₂ by controlled ventilation. Arterial and central venous pressures, CMP, SCP, PaCO₂, PaO₂, and arterial and cerebral venous glucose and oxygen were measured intermittently. rCBF was estimated by brain ¹³³Xe clearance after carotid injection. After a control period, the ascending aorta and superior and inferior venae cavae were clamped for 15 minutes via right thoracotomy. PI arterial pressure was restored and maintained by I.V. levophed infusion.

After the PI hypoperfused state was attained, CPP or Pa(O₂) were varied, and rCBF measurements were made after five minutes at a given Pa(O₂) or after a stable CPP was obtained.

CMP and SCP attained peak pressures between five and ten minutes PI. No significant pressure gradients were observed. Marked reactive hyperemia correlated with the rise in SCP and CMP. Forty-five minutes PI, rCBF was about 50% of control.

PI rCBF did not vary with Pa(O₂). Elevation of CPP did not alter rCBF except at high CPP where in some cases it markedly increased.

At 15 minutes PI, CMRG was significantly elevated while CMRO₂ was unchanged. After 30 minutes, CMRO₂ and CMRG were both generally subnormal with a relatively greater fall in CMRG.

(1) PI brain swelling and cerebral herniation are unlikely since increase in SCP and CMP were moderate and transient without appreciable gradients. (2) The concept of mechanical obstruction of brain vessels as the cause of brain hypoperfusion postischemia is supported by the lack of rCBF response to CO₂ and the variable response to CPP. (3) At 15 minutes PI, brain glucose resaturation occurs. Subsequently, the relatively greater fall in CMRG compared to CMRO₂ suggests brain metabolism of accumulated lactate or endogenous substrates.

VII-48

An Intrinsic Metabolic Mechanism to Protect the Brain During Progressive Cerebral Ischemia—Bruce DA, Schutz H, Vapalahti M, Gunby N, Langfitt TW (Neurosurgery Division, University of Pennsylvania, Pittsburgh, Pennsylvania)

Sixteen mongrel dogs anesthetized with nitrous oxide and oxygen, paralyzed and ventilated to a PaO₂ of 38 to 42 mm Hg, were used in these experiments. CBF was continuously measured by the torcular venous outflow technique, and arterial and cerebral venous blood samples were measured for P O₂, P CO₂, pH, O₂ saturation, glucose, and hemoglobin. Brains were weighed at the completion of each experiment and CBF expressed in milliliters per 100 gm per minute. The cerebral perfusion pressure (CPP) was changed in 10 mm Hg increments by an infusion of mock CSF through a double-barreled needle in the cisterna magna. After each change in CPP ten minutes was allowed for stabilization before blood sampling. CMRO₂ and CMR G₁ were calculated in the standard manner.

During the control period mean CBF was 39 ± 2.37 (SD) ml/100 gm per minute, CMRO₂ 4.64 ± 0.75 ml/100 gm per minute, CMR G₁ 7.73 ± 1.66 ml/100
gm per minute. The oxygen glucose index (OGI = \frac{A - V \text{ Gl}}{A - V \text{ O}_2} \times 100 \text{ mM/L}) was 85%. As the flow fell to 29 ± 2.4 ml/100 gm per minute, 75% of control, there was a fall in CMR Gl G1 to 6.50 ± 1.77 (N.S.) and in CMRO\(_2\) to 3.48 ± 0.62 (P < 0.05) with an OGI of 80%. As the flow fell further to 21 ± 2.77, 50% of control flow, CMR Gl G1 fell further to 4.57 ± 1.5 (P < 0.001). CMRO\(_2\) fell to 2.57 ± 0.55 (P < 0.005) and the oxygen glucose index remained the same at 88%. A further drop of the flow to 14 ml/100 gm per minute, 35% of control, caused a rise in CMR Gl G1 to 5.22 ± 2.49. CMRO\(_2\) fell to 1.77 ± 0.60 and the OGI now fell to 61%. The arteriovenous difference (AVD) for oxygen and glucose which had been fairly constant until this point rose, respectively, to 13.13 vol % from 12.50 vol % and to 35 mg % from 21 mg %. Finally, at a flow of 8 ml/100 gm per minute the CMR Gl G1 was 4.70 ± 2.20, the CMRO\(_2\) 1.14 ± 0.22, and the OGI 42%. The AVDO\(_2\) was 13.62 vol % and the AVD G1 53.5 mg %. Brain temperature was measured by a thermistor under the dura in four dogs, and the maximum fall in temperature was from 36.5°C to 35°C over the period of the experiment.

The results indicate that a mechanism exists that causes a decrease in cerebral metabolism for oxygen and glucose as CBF falls from 75% to 50% of control level. No evidence of ischemia could be identified by the oxygen glucose index in this situation until the CBF had fallen to 35% of control. The reason for the fall in CMR Gl G1 was not substrate limitation. This is shown by the large increase in the A-V glucose difference that occurred at a CBF value of about 35% of control. We suggest that changes occurring within the tissue, possibly on the basis of increasing hydrogen content, lead to alterations in various enzymatic systems and to a general decrease in glucose and oxygen metabolism. Others have demonstrated a normal brain energy charge potential with CBF as low as 50% of normal. These observations combined with the present findings further suggest a decreased ATP turnover rate within the brain.

VII-49 Endothelial Ischemia: Scanning (SEM) and Transmission (TEM) Electron Microscopic Studies—Nelson E, Kawamura J, Sunaga T (Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland)

If it is assumed that events occurring at the luminal surface of endothelial cells may be of importance in ischemia and possible altered permeability of these cells, then a model with reproducible morphological lesions which can be studied by SEM and TEM would be of importance in studies of changes occurring within the tissue, possibly on the basis of increasing hydrogen content, lead to alterations in various enzymatic systems and to a general decrease in glucose and oxygen metabolism. Others have demonstrated a normal brain energy charge potential with CBF as low as 50% of normal. These observations combined with the present findings further suggest a decreased ATP turnover rate within the brain.

VII-50 A Technique for the Assessment of Cerebral Circulation. Re: Cerebral Death—Hoop B Jr, Ames A III, Ojemann RG, Sweet WH, Ackerman RH (Massachusetts General Hospital, Boston, Massachusetts 02114)

Presently employed criteria for cerebral death require that clinical areflexia and electroencephalographical evidence of absent brain function persist for as long as 24 hours. This period of uncertainty as to whether the patient is or is not still alive may raise serious ethical and legal questions for those immediately concerned and may markedly reduce the opportunities of other patients to benefit from organ transplantation. Angiographical studies have shown that irreversible brain damage is associated, quite consistently, with marked impairment of the cerebral circulation. This association could provide an additional, and more rapid, means for establishing the diagnosis of cerebral death. A simple radionuclide tracer technique for prompt, noninvasive assessment of the cerebral circulation has been investigated. Using a single radionuclide tracer which emits gamma radiation of two energies, one too weak to penetrate the skull and the other easily passing through it, tracer activity distributed external to the skull can be distinguished from activity distributed with glutaraldehyde. The opposite carotid was dissected out but not clamped for a sham-operated control. In addition two animals served as unoperated, normal controls. Specimens were prepared in the usual manner for TEM and similarly for SEM except that the latter large vessel segments were not treated with propylene oxide or embedded in Epon, but were air dried and coated with gold palladium. With SEM large numbers of holes or craters were seen distal to the clamp site (and in two specimens in the ipsilateral middle cerebral artery). The clamp site could be identified, and also contained numerous holes, but these lesions were absent or infrequent proximal to the clamp, absent or very infrequent in the sham-operated control, and essentially absent in normal controls. (Preliminary observations indicate identical lesions restricted to branch points in control specimens. If confirmed, this may have considerable physiological and pathological relevance.) It is believed that these are probably nonspecific alterations and can result from ischemia, trauma, and perhaps dietary manipulation. With TEM preliminary observations have shown blebs arising from endothelium and containing swollen pinocytic vesicles from the experimental side, somewhat less frequent structures on the sham-operated side and none in normal controls. In addition, "giant vesicles," probably invaginations from underlying smooth muscle, have been seen on the ischemic side. While it was originally speculated that the TEM equivalent of the craters or holes seen with SEM might be ruptured blebs, further studies using TEM on specimens previously scanned are underway to resolve this important question.

This would appear to be a reproducible model for rapidly and easily studying the effects of ischemia on the luminal surface of vessels, and investigations to see if these lesions can be altered by physiological and pharmacological means are planned.
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within the skull. Following intravenous infusion of an indium-113m-labeled tracer, the count rates from its 392-kev gamma rays and its 25-kev x-rays are recorded separately and analyzed at once by means of a bedside NaI scintillation pulse height spectrometer which views the patient's head. The ratio of the initial count rate of the gamma rays to the x-rays is measured to reflect the ratio of total cephalic blood flow relative to extracranial blood flow. A pilot study was made, in which 13 measurements in ten patients with clinical signs of cerebral death plus electrocerebral silence were compared with 22 measurements in 13 conscious patients. The directly measured ratios demonstrate a statistically significant difference (P < 0.001) between the comatose and conscious patients, with no overlap between the two groups. Taking into account corrections for nonuniform detection efficiency and Compton scattering contributions, the flow ratio indices are expressed as ratios of absolute flow which demonstrate a fourfold difference in relative intracranial blood flow between the groups. Tentatively it is our impression that this technique may prove to be one of the most atrractive and fastest means of diagnosing cerebral death with the required certainty.


The present study was carried out in La Paz (3,750 M). Sixty-seven young, healthy male volunteers were studied. They had been born and permanently residing at a high altitude. Cerebral blood flow (CBF) was measured by the $^{1}$Kr technique. Multiple blood samples were drawn from the brachial artery and the jugular bulb to build washout curve and to measure O$_2$ and CO$_2$ content and partial pressure, pH, hematocrit, blood sugar and lactate. In 24 subjects, cisternal fluid also was sampled. Measurements were made in normal resting (sitting and supine) conditions, during voluntary hyperventilation and while the subject was breathing various mixtures to alter either PAO$_2$ or PACO$_2$.

As compared to sea level data, the most important first findings are: the reduction of CBF, the widening of cerebral O$_2$ arteriovenous differences, and the identity of the local O$_2$ consumption, at least in supine subjects. In the sitting position O$_2$ uptake is slightly reduced and glucose and lactate arteriovenous differences are enlarged. CBF as a function of PAO$_2$ describes a similar curve, but with a higher set point, so that CBF in highlanders is higher than it would be in lowlanders for the same PAO$_2$. Correction of altitude hypoxia decreases CBF below the corresponding sea-level value. Conversely breathing low oxygen mixtures increases CBF.

The acid-base parameters in CSF at rest and their modifications during inhalation of various mixtures will be described and the respective PAO$_2$, PACO$_2$, and CSF pH influences on CBF will be discussed.

RESERVE
Factors Improving Post-Ischemic Cerebral Vascular Obstruction—Cantu RC (John Cumming Building, Concord, Massachusetts)

The occurrence of cerebral vascular obstruction after periods of complete cerebral ischemia has been studied in the rabbit. A variety of physiological, pharmacological, and metabolic factors individually and in combination were studied. Hypertonic solutions of glucose or mannitol most dramatically reduced obstruction, but hypercapnia as well as heparin and HCO$_3$ together also were significantly effective. Factors without a significant effect on obstruction included: tris buffer, HCO$_3$, low molecular weight dextran, glucocorticosteroids, hypercapnia, hypoglycemia, isotonic saline, coumadin, fibrinolysin, papavarnine, vasodilan, sere, and dipyridamole.

In studies using a reversible ischemia model, the occlusive postischemia changes were found to be largely reversible when a flow of oxygenated blood is reestablished at normal pressures. Moderate hypertension in the postischemia period accelerated the reversal of obstruction, 15 minutes of hypertensive reflow being comparable to 120 minutes of normotensive reflow.

The authors infer from the findings of this research that the controlling factor in the brain's ability to survive ischemia is the length of time it takes the cerebral vasculature to become irreversibly occluded, and not the time which brain parenchyma can endure ischemia if O$_2$ and glucose are quickly restored as has been previously supposed.

SUMMARY: D. Lübbers

Session VIII: ICP and CBF
THURSDAY (4:00 TO 5:45 P.M.)
CHAIRMAN: M. BROCK
CO-CHAIRMAN: B. JENNETT
VIII-52 The Effect of the Hydrocephalic Process on Cerebral Blood Flow in the Cat—DiMattio J, Hochwald GM, Malhan C (Department of Neurology, New York University Medical Center, 550 First Avenue, New York, New York 10016)

It has been demonstrated that in normal animals cerebral blood flow (CBF) is to a large extent independent of intracranial pressure. However, cerebral blood flow decreases when the intracranial pressure is elevated to values approaching arterial pressure of the animal. It is not clear whether this relationship also exists in experimental obstructive hydrocephalus where the ventricles are not in direct communication with the subarachnoid space.

In cats with experimental obstructive hydrocephalus the acute and chronic stages of this disease are associated with differences in intraventricular pressure.

The acute stage occurs approximately seven days after the intracisternal injection of kaolin and is characterized by an increase in CSF pressure (range 20 to 35 cm H$_2$O). It has been demonstrated in these animals that the increased pressure is due to a decrease in the cerebrospinal fluid (CSF) absorption capacity. In the chronic stage, in spite of the complete obstruction between the ventricular system and the subarachnoid space, the CSF absorption increases and the CSF...
pressure returns to the normal range. In the present study an attempt was made to correlate the changes in CSF dynamics in acute and chronic hydrocephalic cats with regional cerebral blood flow. Moreover, the effect of the naturally occurring increased intraventricular pressure on CBF also was examined in this experimental pathological preparation.

Total and regional CBF were measured by the indicator fractionating technique using 4-iodoantipyrrine (1I131) as the freely diffusible indicator substance. Regional blood flow was calculated as the product of fractional uptake in the brain of the tracer substance and the cardiac output. The cardiac output was measured in each animal with cat serum albumin (1I125) by nondiffusible indicator dilution technique. Total brain blood flow was determined by summing indicator uptake in the various brain sections. The results are tabulated below. These values were obtained from 21 animals (table).

These results indicate that in the acute hydrocephalic cat there is a 20% decrease in total CBF. This decreased blood flow is fairly well distributed throughout the brain; however, periventricular tissue demonstrates an even greater decrease of blood flow. In the chronic hydrocephalic cat CBF increases to nearly 95% of normal. The brain stem, however, recovers to only 88% of normal. These results demonstrate that autoregulation of CBF may be impaired in acute feline hydrocephalus, but it is not clear whether this precedes or follows changes in CSF dynamics.

**VIII-53 Comparative Effects of Increased Intracranial Pressure Upon Cerebral Oxygenation, Cortical Evoked Potential and Brain Survival—Clague B, Lorig RJ, Weiss MH, Nulsen FE, Brodkey JS (Department of Neurosurgery, Case Western Reserve University, Cleveland, Ohio)**

We have sought to define, with increasing intracranial pressure, that point at which brain dysfunction and death are threatened. Is there a critical level of cerebral perfusion pressure or do other monitoring parameters provide more reliable early warnings?

In 17 awake dogs monitored intracranial pressure was manipulated by gravitational ventricular infusion. Arterial pressure and PtO2, lateral sinus PO2 and oxygen saturation (SO2) and A-V lactate differences, cortical visual evoked potential (CEP), and EEG were all monitored along with animal survival. The animals were ventilated and end-tidal Pao2 was maintained constant.

Striking correlation exists between changes in the CEP, EEG and lateral sinus PO2. Increased intracranial pressure that allowed a lateral sinus PO2 of 40 mm Hg or greater could be sustained for more than four hours with no appreciable change in electrical parameters or animal survival. For PO2 between 20 and 40 mm Hg a period of less than two hours existed when changes in the late wave form of the CEP were followed by abrupt loss of the CEP and EEG. These changes related to SO2 decreases below 30% and were readily reversible with improvement in cerebral perfusion. At venous PO2 of less than 20 mm Hg, CEP and EEG changes occurred rapidly. Significant lactate differences occurred during these periods of lowered PO2. Duration of absent CEP and EEG (less than five minutes) determined animal survival. Perfusion pressure showed poor absolute correlation with the development of CEP, EEG, and venous PO2 worsening; but the duration of marginal perfusion was a significant factor in the outcome.

**VIII-54 The Relationship Between Cortical Electrical Activity, Cerebral Perfusion Pressure and Cerebral Blood Flow During Increased Intracranial Pressure—Grossman RG, Turner JW, Miller JD, Rowan JO (Institute of Neurological Sciences, Glasgow, and the Albert Einstein College of Medicine, New York)**

The relationship between neurophysiological function in the cerebral cortex and intracranial pressure (ICP) was examined in seven anesthetized baboons, with reference to cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). An electrode system was mounted over the occipitoparietal cortex for stimulating and recording the direct cortical response (DCR). ICP was increased by infusion of mock CSF and measured from the lateral ventricle or cisterna magna. CBF was measured by the intracarotid 133Xe technique.

The effect of increased ICP on the amplitude of the DCR was not direct, but was related to the difference between arterial and intracranial pressure, CPP. For the pooled results there was a significant correlation between percentage change in CPP from control (x) and percentage change in DCR amplitude (y), the regression equation being: y = 0.87 x + 10.8; r = 0.62, P < 0.001.

The correlation between CPP and DCR amplitude was closest when autoregulation was impaired, so that CPP and CBF bore a linear relationship to each other.

Thus there was a closer correlation between CBF and DCR amplitude. The regression equation relating percentage change in CBF from control (x) with percentage change in DCR amplitude was: y = 1.51 x – 56.8; r = 0.90, P << 0.001. The regression line intersects the zero axis for DCR amplitude at 39% of control CBF. The CBF results refer to mean (H/A) flow; changes in fast component flow could only be closely correlated to DCR amplitude if the weight of the fast component was considered also.

<table>
<thead>
<tr>
<th>Type of animal</th>
<th>Mean CBF</th>
<th>Cerebellum</th>
<th>Brain stem</th>
<th>Cerebrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>136.1*</td>
<td>146.5</td>
<td>115.4</td>
<td>139.4</td>
</tr>
<tr>
<td>Acute hydrocephalic</td>
<td>109.6</td>
<td>118.8</td>
<td>95.8</td>
<td>111.1</td>
</tr>
<tr>
<td>Chronic hydrocephalic</td>
<td>129.3</td>
<td>136.1</td>
<td>106.3</td>
<td>132.2</td>
</tr>
</tbody>
</table>

*All values are ml/min/100 gm dry brain weight.
SYMPOSIUM ABSTRACTS

It is concluded that the effects of increased ICP on neurophysiological function in the cerebral cortex are mediated through changes in CBF, and that a reduction in CBF to less than 40% of control, produced by reduced CPP, is sufficient to abolish the direct cortical response.

VIII-55
Differential Pressures Recorded in Acute Epidural Expanding Lesions; Correlation With Local Cerebral Blood Flow by Hydrogen Clearance in Baboons—Symon L, Pasztor E, Dorsch NW, Branson NM (Department of Neurosurgical Studies, Institute of Neurology, Queen Square, London, England)

Six anesthetized baboons have been studied with epidural pressure transducers in both frontal and parietal zones, hydrogen polarographic electrodes in frontal and parietal cortex, putamen and white matter on both sides, and an extradural balloon placed in the right occipital zone. Cisternal pressure also has been recorded by needle and strain gauge.

After preliminary stabilization and testing of CO₂ reactivity, the epidural balloon has been expanded at a rate of 0.2 ml per minute, the continuous infusion being interrupted to maintain constant pressure during recurrent episodes of hydrogen clearance to three-minute hydrogen inhalations.

Clear evidence of a pressure gradient highest in the right parietal and lowest in the left parietal zone have been obtained, so that by the time of the attainment of massive herniation with bilateral fixed dilated pupils, differential pressures between the right side of the head and the left have amounted to between 16 and 30 mm Hg to balloon inflation from rest to coning and near circulatory arrest in between 40 and 120 minutes (usually a 60-minute period was used). With more rapid balloon inflation, differentials of up to 60 mm Hg have been observed.

Despite the clear evidence of a gradient of pressure in the epidural space, flow data have shown that those electrodes undisturbed by distortion of the brain have shown continued regulation on both sides of the head until a gross rise in intracranial pressure had occurred, when there has been evidence of an inflection in the autoregulatory flow pattern at roughly the same time throughout the head, so that the differential pressures do not appear to have been accompanied by differential flow failures. The significance of this will be discussed.

Following the experiments, the heads have been fixed in situ with the balloon inflated, and the pattern of midline and foraminal herniation examined.

VIII-56
Intracranial Pressure Gradients and Cerebral Hemispheric Blood Flow Differences During Expansion of Unilateral Supratentorial Mass Lesions in Primates—Johnston IH, Rowan JO (Institute of Neurological Sciences, Wellcome Surgical Research Institute and Regional Department of Clinical Physics and Bioengineering, Glasgow, Scotland)

Seven adult baboons each weighing about 10 kg were used. Anesthesia was induced with phencyclidine hydrochloride (10 mg) and sodium thiopentone (60 mg) and maintained with a combination of phencyclidine hydrochloride and suxamethonium and a nitrous oxide/oxygen mixture. A Starling pump was used to control ventilation.

Systemic arterial pressure (SAP), right and left ventricular fluid pressures (RVFP and LVFP), and right and left subdural pressures (RSDP and LSDP) were monitored continuously using indwelling catheters and strain gauge transducers. The cerebral blood flow (CBF) in each hemisphere was measured at intervals using the ¹³³Xenon clearance technique. The CBF measuring equipment employed two one-half-inch diameter sodium iodide scintillation detectors accurately collimated to define each cerebral hemisphere with no more than 5% "cross talk."

A balloon was inserted into the right subdural space supratentorially and inflated so that the intracranial pressure (ICP) was raised in steps of 15 to 20 mm Hg every 30 minutes up to 90 mm Hg. The various pressure differences across the head and the CBF in each hemisphere were measured at each level of ICP.

The paired "t" test showed that there was no significant difference between the pressures in each lateral ventricle (t = 1.46, number of paired observations n = 51, P > 0.1). The mean pressure difference pd = 0.5 mm Hg and the maximum recorded pressure difference pd_max = 5 mm Hg.

RSDP and LSDP were compared in three animals. RSDP never exceeded LSDP by more than 7 mm Hg. The paired "t" test again indicated that there was no significant difference between the pressure measurements (t = 1.5, n = 19, P > 0.1). Although the balloon was inflated on the right, on the average LSDP was higher than RSDP (pd = 1.2 mm Hg).

RSDP and LVFP were compared in four animals. RSDP never exceeded LVFP by more than 9 mm Hg. The paired "t" test showed that despite the fact that the balloon was on the right, LVFP was higher on the average than RSDP (pd = 2.4 mm Hg) and that this difference was just significant (t = 2.64, n = 25, P < 0.05). This indicates the small systematic error which can be present when subdural pressure is measured.

In five animals the CBF in each hemisphere never differed by more than 12 ml/100 gm per minute. In one animal the hemisphere difference only rose above 14 ml/100 gm per minute when the perfusion pressure fell to a level around 10 mm Hg and the right hemisphere CBF fell almost to zero. In the other animal a hyperemia developed in the left hemisphere. The paired "t" test carried out on all results showed that there was no significant difference in hemisphere CBF (t = 1.5, n = 48, P > 0.1). On the average the left hemisphere CBF exceeded the right hemisphere by 2.3 ml/100 gm per minute.

In summary, when a right supratentorial balloon was inflated up to ICP levels of 90 mm Hg no significant right to left pressure gradients nor significant hemisphere CBF differences were recorded.
Intracranial Pressure, Cerebral Blood Flow and Prognosis in Patients With Severe Head Injuries—Kelly PJ, Iwata K, McGraw CP, Tindall GT (University of Texas Medical Branch, Department of Surgery, Galveston, Texas)

Forty-one patients with severe head injuries and in varying grades of coma were admitted to our Closed Head Injury Unit and their intracranial pressure (ICP) was monitored by means of a subdural or epidural transducer or a catheter placed in a lateral ventricle. ICP was considered elevated when it exceeded 22 mm Hg over 50% of the time in any 24-hour period and was treated with the administration of 500 cc of a 20% mannitol solution intravenously over a one-hour to two-hour period.

At some time less than two weeks after the acute head injury, cerebral blood flow (CBF) was measured in 17 patients by the 85Kr desaturation technique of McHenry. CBF of 56 ml/100 gm brain per minute ± 7 ml was considered normal. Retrospectively, patients were classified as to the eventual outcome of their injury and an attempt was made to correlate the result with the measured levels of CBF and ICP.

Though the results of CBF data on 17 patients can hardly be considered conclusive, it was noted that all patients who had a normal CBF recovered to a satisfactory level. All patients who expired or survived in a vegetative state had a low CBF. The combination of a low CBF and high ICP resulted in a poor prognosis. These data suggest that head-injured patients who are able to maintain a normal CBF, particularly when ICP is elevated, have better prognoses than patients with low CBF.

The prognosis was not related to ICP provided that elevated ICP was treated aggressively in the manner outlined above.

On the basis of our results and those reported in the literature (Vapalahti and Troupp), it appears that traumatic cerebral edema can be treated effectively and survival significantly improved if treatment is directed at elevating CBF. This is based on the observation that when CBF is elevated, brain tissue nutrition is improved and neuronal death is decreased. Also, it is observed that when ICP is elevated, cerebral blood flow is decreased, and this appears to be a cause rather than an effect of increased ICP.

Intracranial Pressure, Cerebral Blood Flow and Prognosis in Patients With Severe Head Injuries—Kelly PJ, Iwata K, McGraw CP, Tindall GT (University of Texas Medical Branch, Department of Surgery, Galveston, Texas)

Regional CBF and intraventricular fluid pressure (MIVP) were measured in ten patients with severe brain injury, mainly traumatic, in the control state and during functional tests of the cerebral circulation. Regional CBF was determined serially by the intraarterial Xenon washout method, mean arterial blood pressure (MABP) was recorded from the carotid artery catheter, while MIVP was recorded from a catheter in the lateral ventricle. Cerebral perfusion pressure (CPP) was defined as MABP-MIVP. Autoregulation to an increase in CPP was tested by measuring the rCBF response to transient systemic hypertension produced by an infusion of angiotensin, and CO2 responsiveness was similarly tested during artificial hyperventilation.

When autoregulation was impaired MIVP rose simultaneously with MABP during induced hypertension, particularly if the resting level of MIVP was elevated. Intact CO2 responsiveness to moderate hypocapnia (Pc02 20 to 25 torr) was observed in patients with impaired autoregulation, and in these a reduction of MIVP was seen during hyperventilation. Since the CPP was changed by hyperventilation, the rCBF predicted at that CPP on the basis of a pressure passive response with the same slope as measured during the hyperventilation test was calculated. The difference between this calculated value and the measured rCBF was defined as the response to CO2. Moderate hyperventilation had no effect on MIVP in two patients with impaired CO2 responsiveness. In one case MIVP remained elevated above the control level after the hyperventilation test and was refractory to moderate hyperventilation.

The control level of rCBF in these patients was variable, focal abnormalities were observed in 40%, and shunt peaks were seen only over the major arteries. The above response patterns will be illustrated by the presentation of individual case reports.

We believe that these cases firmly support the thesis that impaired cerebral circulatory regulation and systemic hypertension is an important mechanism in the development of cerebral edema in brain-injured patients.

Cerebrovascular Response Pattern During CO2 Rebreathing—North B, Jennett S (Departments of Neurosurgery and Physiology, University of Glasgow, Scotland)

Rising PaaCO2 during brief rebreathing causes a linear increase in ventilation which is taken to parallel a rise in medullary extracellular acidity (Read and Leigh, 1967). It also causes an increase in cerebral blood flow, and if this too is related to changing extracellular acidity it should show a similar latency and linearity to the ventilatory response. Intracranial pressure (ICP) also increases consequent on vasodilatation as PaaCO2 rises, and the rate of increase in ICP will reflect both cerebrovascular reactivity and the compliance of the intracranial contents.

We have made observations in patients with a variety of types of acute brain damage, in whom the ICP was being monitored continuously. Simultaneous records were made of ICP with tidal volume and breath by breath minute volume, CO2 % at the mouth and arterial blood pressure, during air breathing and during two to three minutes' rebreathing from 6 liters 6% to 7% CO2 in oxygen. In 22 tests ICP started to rise after a latency ranging from 10 to 120 seconds, but usually within 10 seconds of the corresponding start of the increase in ventilation.

Values were found for mean PaaCO2 and for mean ICP for each period of 10 to 15 seconds during rebreathing. These mean values (in mm Hg) were plotted and showed a linear increase in ICP with rising PaaCO2 (correlation coefficient > 0.9). The slope of the regression line ranged from 0.7 to 8.6 for ΔICP/ΔPaaCO2. Despite a
IX-59
Cerebral Autoregulation: Regional Cerebral Blood Flow and Cardiohemodynamic Measurements—McHenry LC Jr, West JW, Cooper ES, Goldberg HI (Stroke Research Center, Philadelphia General Hospital, Philadelphia, Pennsylvania)

The presence or absence of cerebral autoregulation in stroke could have therapeutic importance, and hence should be determined whenever possible. Autoregulation was tested by regional cerebral blood flow (rCBF) and cardiohemodynamic measurements before and after induced systemic arterial hypertension in 16 patients with varying neurological disorders. Hypertension was induced by increasing the arterial blood pressure by an intravenous infusion of Aramine (50 mg in 250 ml of saline). Seven (Group 1) of the patients had a mean increase in mean arterial pressure (MAP) of 32 mm Hg and had preserved autoregulation, while nine (Group 2) with a 56 mm Hg increase in MAP showed complete or mixed loss of autoregulation. The response to 5% CO2 inhalation also was tested in 14 of the patients (during CO2 inhalation the MAP increased a mean 10 mm Hg in Group 1 and 25 mm Hg in Group 2). Group 1 had a higher control or baseline mean CBF (41 versus 36 ml/100 gm per minute, respectively) than did the group with loss of autoregulation. The group with loss of autoregulation also generally had more severe involvement on the cerebral angiogram than did the other. Baseline cardiac index and cardiac work were lower (1.91 versus 2.84 l/m²/minute and 4.7 versus 7.4 kg-m/minute) in the group with loss of autoregulation. The mean CBF response to hypercapnia (51% versus 36%) was greater in the group with preserved autoregulation.

During Aramine infusion the MAP was increased by 38% in Group 1 and 59% in Group 2. The mean CBF was essentially unchanged in Group 1 but increased 24% in Group 2. CI and CW changed less (4% and 56%) in Group 1 than in the group with loss of autoregulation where the CI and CW increased 31% and 126%. When autoregulation is lost, rCBF may increase homogeneously or heterogeneously with some areas increasing while others remained unchanged or even decreased. In four instances there was an intracerebral steal during induced hypertension with a fall in rCBF.

Whether or not autoregulation is preserved could be related to: (1) the greater induced increase in MAP in Group 2 than Group 1, (2) greater angiographical involvement with a lower baseline in CBF in Group 2 than Group 1, or (3) a direct or indirect influence of various cardiovascular factors.

IX-60

In 32 patients suffering from cerebrovascular disease of acute onset but different severity (ranging from transient ischemic attack to completed stroke) regional cerebral blood flow (rCBF) was measured using the scintillation camera and intracarotid 133Xe. The obtained hemispheric and focal flow values were compared to the findings of brain scintigraphy with 99 m Tc-pertechnetate performed 5 to 30 days after the onset of the cerebrovascular attack. According to the detectability of lesions by brain scintigraphy the patients were categorized in three groups. CBF values in the hemisphere and in the clinical focus were studied in each group:

1. In 17 patients scintigraphy showed clear to massive foci. Mean hemispheric blood flow was 30 ml/100 gm per minute; average flow within the foci was decreased to 23 ml/100 gm per minute.
2. In four patients isotope uptake was slightly increased within the focal lesions. In these cases hemispheric flow was 39 ml/100 gm per minute, and focal flow was 29 ml/100 gm per minute.
3. In 11 patients no foci were detected in the scintiphotos, but regional abnormalities were found in the rCBF maps. Average hemispheric flow in this group was 39 ml/100 gm per minute, and focal flow was found to be 32 ml/100 gm per minute.

It may be concluded from these data that rCBF of 29 ml/100 gm per minute represents the lowest level of sufficient perfusion for preserving the morphological integrity of the tissue. Flow values below this borderline indicate a lack of blood supply leading to an altered permeability of the vessels and to an impairment of the anatomical structures visible in the scintiphotos.

IX-61
rCBF in Cerebral Infarction—Fieschi C, Battistini N, Bertini G, Bozzao L, Fumagalli C, Prencipe M, Nardini M, Nori A, Antonini FA (Department of Neurology, University of Siena; Department of Geriatrics, University of Florence; Department of Neurology, University of Rome, Italy)

Twelve patients with acute focal cerebrovascular lesions (brain infarcts) were studied with measurements of rCBF coupled with CSF pressure recordings.

Conditions for admittance to the study were acute onset (within 36 hours), location in the carotid territory, absence of carotid occlusion or stenosis at angiography, compensated cardiorespiratory state. Ipsilateral rCBF was measured with eight probes with the 133Xe intracarotid injection technique. rCBF was measured at normocapnia and resting MABP, followed by a test repeated during 5% CO2 inhalation and during 20 mm Hg change in MABP. In four of the cases the study was repeated 24 hours later.

Besides recording or measuring the arterial $P_{O_2}$ and $P_{CO_2}$ and BP, in all patients the lumbar CSF pressure was continuously recorded, adequate time being allowed to reach steady state under the different test conditions.
Aim of this study was to verify the existence of paradoxical CBF responses to carbon dioxide and MABP changes, and to correlate them with concomitant changes in intracranial pressure, indirectly derived from lumbar CSF pressure.

Autoregulation was impaired in the totality of patients, in one or more regions; CSF pressure changes were of the same order of magnitude as MABP changes only in two cases of global loss of autoregulation. In the remaining cases there was a scattered correlation between loss of autoregulation and CSF pressure changes, while in no case we observed parallel changes on MABP and CSF pressure in the absence of CBF variations. This was in contrast with the occurrence of "false autoregulation" in focal cerebrovascular pathology.

To be examined is the reason for persisting increase of CBF after release of a temporary rise in MABP; in relation to the concepts of CVR.

The inhalation of CO₂ constantly induced CSF pressure changes in the same direction, although the cerebrovascular reactivity in the diseased hemisphere varied considerably. Therefore CSFP changes did not serve to anticipate or to explain the different modes of focal reactivity to CO₂ inhalation. It is concluded that if local pressures are involved in producing paradoxical "steal" responses, those changes in pressure are not significantly reflected in the measurement of lumbar CSF pressure.

IX-62
Studies of rCBF on Neuropsychological Disorders Caused by Acute Cerebrovascular Accidents in the Major Hemisphere—Kohlmeyer K (Neurological Clinic, University of Giessen, FRG)

In 100 patients suffering from different types of speech disorders and other neuropsychological symptoms (alexia, agraphia, acalculia) caused by acute focal cerebral circulation disorders rCBF studies were performed by means of the intracarotid ¹³³Xe method using 16 scintillation detectors. The 16 values were calculated according to the initial slope index. The studies were performed 3 to 14 days after the onset of the ischemic stroke. Each case had undergone carotid angiography (CAG) one day before the rCBF measurement. The rCBF investigations were carried out under local anesthesia and (1) in the resting state, (2) in hypocapnia or hypercapnia by means of active hyperventilation or CO₂ inhalation, and/or (3) in hypertension to test autoregulation.

Arterial focal ischemic or hyperemic lesion is defined in our studies by flow values being 15% below or above the hemispheric mean value, measured by two or more neighboring detectors.

A P<sub>CO₂</sub> was determined during each study.

In 59 of 100 patients the CAG was normal. In 36 patients the CAG revealed an occlusion in the trunk of the middle cerebral artery (five) or in one or two branches of the MCA (31).

In five patients a subarachnoid hemorrhage occurred accompanied by severe spasm in the MCA.

The following results were obtained in rCBF studies:

- Mostly a small ischemic focus was found in the frontal, parietal or temporal region in cases of motor, nominal-conduction or sensory aphasia. Disorders of writing, reading and calculating revealed a focus in the parieto-occipitotemporal region. Exceptions (5%) from these general findings are discussed.

In cases of total aphasia the focus represents the whole supply of MCA or the large region round about the Fissura sylvii.

There was no difference in the site and in the enlargement of the focus in the groups with and without arterial occlusion.

In some cases the focus became larger in the functional tests and indicated a local functional circulation disorder in the borderlines of an ischemic centrum.

Some meanings for the pathogenesis of local cerebral ischemia with and without pathological findings in CAG and for the aphasiology are discussed.

IX-63
Relationship Between Different Levels of CBF and Reactivity to Physiological Stimuli (CO<sub>2</sub> and MABP)—Pistolesi GR (Second Surgical Clinic, University of Rome, Italy), Faraglia V, Spartera C, Tata MV, Agnoli A

To determine the critical flow level during carotid clamping it is useful to establish what CBF levels cause a change in the reactivity to physiological stimuli.

The carotid clamping used during the first trial testing of carotid endarterectomy is able to cause an ischemia that could be considered similar to an experimental ischemia.

During carotid clamping CBF decreases to different levels depending on the efficiency of compensatory mechanisms. Under these conditions, the reactivity to physiological stimuli, with special reference to P<sub>CO₂</sub> and arterial pressure changes, was studied for each CBF level. These tests also were conducted on patients not subjected to carotid clamping.

Twenty-five patients with cerebrovascular insufficiency due to carotid obstructions and averaging 60 years of age have been studied. The CBF was examined during carotid surgery. It was measured with ¹³³Xe in basic conditions and during clamping, and under different physiological stimuli such as variations in the arterial P<sub>CO₂</sub> and arterial pressure, for a total of 62 analyses.

Patients were ventilated with 50% O<sub>2</sub> and 50% N<sub>2</sub>O, 0.5% methoxyfluorane. Hypercarbia was obtained by adding a 10% mixture of CO<sub>2</sub>. Hypocarbia was obtained by hyperventilating patients. Hypertension was obtained by means of an angiotensin infusion.

Lower rCBF values were obtained during carotid clamping.

The normal reaction to CO<sub>2</sub> increase is lost or inverted for CBF values under 30 ml/100 gm per minute.

The response is absence in four analyses with basal flow over 50 ml/100 gm per minute even if the vessels had already been maximally dilated.

The vasoconstrictive response to hypocarbia slowly tends to fall to values of 30 ml/100 gm per minute or less even though it is always present.

The CBF response to increased values in pressure shows that there is loss of autoregulation for CBF values under 30 ml/100 gm per minute. Autoregulation is conserved in all other situations.
SYMPOSIUM ABSTRACTS

From these data result that: (1) an ischemia of even brief duration (two minutes) can disturb vasomotor reactions; (2) this occurs when definite flow levels equal to or less than 25 to 30 ml/100 gm per minute are reached; and (3) the vasoconstrictive capacity is, for all purposes, preserved during clamping ischemia in that hypocarbia can produce its effect even at low flow levels.

IX-64
Preoperative and Postoperative Cerebral Blood Flow in Patients With Carotid Artery Stenoses—Herrschft H, Duus P, Gleim F, Ungeheuer E (Departments of Neurology, Surgery, and Anesthesiology, Akademisches Krankenhaus Nordwest der Johann-Wolfgang-Goethe-Universität, Frankfurt [Main], Germany)

Global and regional cerebral blood flow was measured in 56 patients with stenosis of internal carotid artery. Forty-three patients had episodes of transient cerebral ischemia; 12 of these and 13 others had cerebral infaracts with slight or moderate neurological deficits.

rCBF studies were performed by the intra-arterial isotope clearance method, using the 10 detector equipment of Siemens. rCBF values were calculated by a computer program. Prior to rCBF investigations the morphological picture of the cerebral vessels were studied by four-vessel angiography. During CBF measurements arterial P CO 2 , P O 2 and pH were determined. Blood pressure was continuously controlled.

In all cases the constriction of the vessel's lumina surmounted 70%. The global cerebral blood flow of the corresponding hemisphere amounted to an average of 38.5 ml/100 gm per minute, i.e., a decrease of 30.5% as compared with normal values (56.5 ml/100 gm per minute—stochastic analysis). In relation to the collateral circulation the decrease of the CBF in the individual case varied considerably between 10% and 60%. The regional blood flow values were altered corresponding to the individual cerebrovascular conditions.

At an interval of three to six weeks after carotid endarterectomy or resection of a “kinking” in 42 patients, there were performed a control angiogram and a second rCBF study. The global CBF average value increased from 39.5 to 48.8 ml/100 gm per minute, i.e., an improvement of 26.8%. In relation to the preoperative CBF value and the condition of the cerebral collateral circulation the global increase of the CBF in the individual case varied between 0% and 45%.

IX-65

Carotid ligation in the neck is still a widely used method of treating certain intracranial aneurysms, and recent studies have confirmed its efficacy. However, it carries the risk of producing ischemia of the ipsilateral cerebral hemisphere, which occurred in 29% of Nishioka’s series of 785 cases and in 43% of Millikan’s 188 patients. In the cooperative study the signs of ischemia were delayed in onset for more than 48 hours in 20% of those affected; and in 44% of 116 patients neurological deficit persisted in spite of release of the ligation. There is need for a technique which will be more reliable than those hitherto available in predicting which patients will not tolerate ligation.

In 1966 we reported ten patients in whom cerebral blood flow (CBF) was measured by the Xenon method before and after trial clamping of the carotid arteries; clinical signs of cerebral ischemia developed only when flow was reduced by > 25%. This method has now been used in 53 patients for whom carotid ligation was planned; 32 were ligated but in the other 21 the procedure was abandoned because of reduction in flow during trial clamping. The incidence of hemiparesis has been significantly reduced since the introduction of this technique to < 10% of those ligated. In recent cases the stump pressure has been measured during temporary clamping and a correlation found between this and the change in CBF. Correlation between changes in EEG record and CBF during trial clamping also has been established.

There was a significant difference in the change in CBF during common carotid clamping as compared with clamping of the internal carotid in > 25% of patients; in half of these a steal down the internal was demonstrated during clamping of the common carotid. This suggested that in such patients permanent ligation of the common carotid might be less safe than ligation of the internal; and in this series the internal carotid was ligated in 18 patients and the common carotid in 14.

The effects of local and general anesthesia also have been explored. Reductions of flow were less marked under general anesthesia and fewer patients developed signs of cerebral ischemia; additional advantages are easier control of Pa CO 2 and less stress to the patient.

We have continued to use 25% reduction as the guideline to the safety of ligature, but this may be modified if the initial flow is unusually high or low.

IX-66
Microvascular Surgery of the Brain and rCBF—Schmidek H, Gratzel O, Steinhoff H, Steude U, Enzenbach R (Institute for Surgical Research, Departments of Surgery and Neurosurgery, University of Munich, Munich, West Germany)

At the Rome CBF Symposium we reported on regional cerebral blood flow (rCBF) studies in seven patients in whom an extracranial-intracranial bypass between the superficial temporal artery and a cortical branch of the middle cerebral artery had been created to improve the blood supply to the ischemic brain. At the time of writing this, the number of patients established with an extracranial-to-intracranial arterial shunt has increased to 31. Twenty-five of them underwent rCBF study by 133Xenon clearance using 16 detectors. In seven patients rCBF was measured only before the operation; four of them have been operated on very recently and will be studied again. In four additional patients the investigation could be done only postoperatively, in part because of occlusion of the internal carotid artery. In another group of 15 patients flow was measured preoperatively and postoperatively. Most of
the postoperative studies were done on the day before discharge from the hospital. But there are now six patients with follow-up studies from six weeks to 18 months following the operation. Including 30 other patients, originally considered for microvascular surgery but not operated on because of a convincing indication for the operation could not be established, this report covers a total of 56 patients and 81 rCBF studies. According to rCBF, postoperative results in 19 patients are classified as follows: (a) blood supply to a previously found ischemic region of the brain markedly improved or restored toward normal (six patients); (b) function of bypass proved (injection of isotope made via external carotid artery) (11 patients); (c) no evidence for function of bypass (two patients). In order to further increase the success rate of this operation, it seems to be mandatory to define the indication for this procedure more precisely. In our experience the best results will be obtained when the operation is performed as a preventive measure in those patients not yet presenting with completed neurological deficits who, however, without treatment are likely to develop symptoms of cerebral ischemia in the future.

IX-67
rCBF Study as a Test in the Management of the Arterial Hypertension—Agnoli A (First Clinica delle Malattie Nervose e Mentali dell'Università di Roma, Italy), Pistolese R, Prencipe M, Faraglia V, Pastore E, Fiorani P
Arterial hypertension is the most important risk factor leading to cerebrovascular disorders. But a reduction of the arterial pressure in some cases can be responsible for cerebral ischemia. The point, therefore, is to determine whether in which cases and to what degree the arterial pressure can be lowered. The study is being performed on patients of different ages with arterial hypertension of various causes (essential, renovascular, pheochromocytoma, etc.) and disorders of the cerebral circulation.

Six patients were studied. The rCBF has been measured with the $^{133}$Xe technique in basal conditions and during hypercapnia in order to test the vessel elasticity, hypotension being induced by Arfonad. The hypotension was about 20 to 30 mm Hg mean pressure (referred to the mean basal pressure). The study includes $P_{CO_2}$, $P_{O_2}$ and pH as well as arterial pressure measurements.

A carotid angiogram was performed about one hour before the observation. The carotid artery was catheterized during the angiography. On the basis of the results obtained the patients can be divided into three groups.

(1) In three cases a reduction of the rCBF occurred during hypotension. In two of these cases the reduction involved the whole region under examination. A reduced response to $CO_2$ was observed. The patients were elderly subjects with arteriosclerotic damage.

(2) In two cases there was no rCBF reduction; the response to $CO_2$ was normal. The patients were rather young hypertensive subjects with no evidence of damage involving other vascular regions.

(3) There was a focal reduction of the flow in one case with no evident damage of other vascular regions. An anomaly of the circle of Willis was observed.

RESERVE
Correlation of Continuous Electroencephalograms With Cerebral Blood Flow Measurement During Carotid Endarterectomy—Sharbrough FW, Messick JM Jr, Sundt TM Jr (Cerebrovascular Clinical Research Center and the Departments of Neurology, Anesthesiology, and Neurosurgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901)

Over an 11-month period 82 endarterectomies operated under general anesthesia were monitored with continuous electrolytechograms (EEG) and cerebral blood flow (CBF) measurements. There was a close correlation between the CBF per 100 gm during carotid occlusion and alterations in the EEG: no change was seen with the blood flow above 30, major changes were not seen with a flow between 18 and 30, and with a flow below 18 EEG changes invariably occurred. The degree of EEG change reflected the severity of flow reduction but was always reversible with the placement of a shunt. The EEG at the termination of the operative procedure corresponded with the patient's neurological state in that all EEGs were normal or unchanged at the termination of the procedure and no neurological worsening was seen during the operative procedure in any patients studied. It is concluded that the EEG offers a valuable monitoring technique that increases the safety of this procedure, indicates when a shunt is required, and informs the surgeon of the state of cerebral function not only during the period of occlusion but from the beginning to the end of the entire operative procedure.

(This investigation was supported in part by Grant NS 6663 from the National Institutes of Health, Public Health Service.)

SUMMARY: J. Meyer

Session X: Clinical Miscellaneous
THURSDAY (11:00 A.M. TO 12:45 P.M.)
CHAIRMAN: C. FIESCHI
CO-CHAIRMAN: O. REINMUTH
X-68
Vasomotor Paresis in Migraine—Simard D (Hôpital de L'enfant Jesus, Quebec, Canada), Paulson OB

The regional cerebral blood flow (rCBF) was measured using the $^{133}$Xenon intracarotid injection technique in a 32-year-old man during an attack of "accompanied migraine." The patient had a total global aphasia and a mild right-sided hemiparesis accompanying the migraine attack. These symptoms lasted for several hours, making the rCBF study possible.

In two previously reported cases by Skinhöj a low rCBF was found, but our case is the first one in which the vasoreactivity could be tested.

Our study revealed an even lower rCBF, the average hemisphere value being 21 ml/100 gm per minute and focal changes were not observed (rCBF was recorded in 35 regions). A repeated resting state revealed an unchanged rCBF with a stable $P_{CO_2}$ at 29 mm Hg. The intravenous injection of ergotamine tartrate (1 mg) did
not change the rCBF. After induced hypercapnia changing the \( \text{Pa}_2 \text{CO}_3 \) from 28 mm Hg to a nearly normal value of 38 mm Hg, the rCBF was unchanged indicating a marked vasoparalysis with regard to \( \text{Pa}_2 \text{CO}_3 \) changes.

Finally, the rCBF was measured after an intracarotid injection of papaverine (10 mg) and an increase in flow from 21 to 37 ml/100 gm per minute was observed. However, the patient's spontaneous \( \text{Pa}_2 \text{CO}_3 \) was now 36 mm Hg and this might indicate a change in the migraine attack as the patient was recovering. One hour later this patient had a strictly normal neurological examination.

A repeated rCBF done a few days later showed a strictly normal rCBF and vasoreactivity in this patient.

X-69
Abnormalities of rCBF in Chronic Schizophrenia With Mental Deterioration—Ingvar DH, Fränzén G (Department of Clinical Neurophysiology, University Hospital, and the Department of Psychiatry II, Sankt Lars Hospital, Lund, Sweden)

Twenty patients were studied, one young group, four women and seven men (mean age 24.5 years [17 to 24]), and one older, nine women (mean age 61 years [49 to 72]). Mean duration of the disease was 5.5 years and 39.7 years, respectively. All patients showed classical symptoms of schizophrenia with cognitive and emotional disturbances and hallucinations. The young patients were well preserved intellectually. All the older ones showed advanced symptoms of so-called schizophrenic dementia with autism, bizarre behavior, symptoms of catatonia, etc. rCBF was measured at rest and during mental activation with \(^{133}\text{Xenon} \) using a 32 detector equipment and a small computer.

Both groups showed normal mean rCBF variables \( f (m), f (i), f (a), f _{p} \), and g %). In the young group some correlations could be established between the degree and type of psychosis and the flow level. The regional flow distribution was largely normal in the young group. In the older ones, the flow in frontal regions was relatively low and, in many cases, relatively high occipitotemporally. Mental activation in the young group (Raven's matrices) gave normal flow augmentations within expected regions (intrinsic cortex). In the most autistic older patients only very slight flow changes, if any at all, were recorded occipitally in connection with a simple picture test. Some of the older patients with whom contact was established, however, did show normal flow changes during the same test.

The finding of a normal mean cerebral blood flow and normal relative weight of the gray matter in an old group of chronic schizophrenics with advanced intellectual deterioration demonstrates clearly that this type of dementia differs fundamentally from organic dementia of corresponding severity (Alzheimer's disease, post-traumatic dementia), when the cerebral oxygen uptake and blood flow as a rule are highly reduced. The relatively low frontal flows in schizophrenic dementia indicate a low activity (arousal) within brain regions which normally are responsible for the structure and goal direction of the psychic activity. Possibly, the relatively high flows occipitotemporally within the same group are related to ongoing hallucinatory activity. The lack of rCBF changes during attempts to mental activation supports current hypotheses that mental deterioration in chronic schizophrenia may be due to, or is accompanied by, a defective arousal by complex sensory stimulation.

X-70
Cerebral Blood Flow, Cerebral Metabolic Rate of Oxygen and CSF Acid-Base Parameters in Patients With Acute Pyogenic Meningitis and With Acute Encephalitis—Paulson OB (current address: Department of Neurology, Mayo Clinic, Rochester, Minnesota 55901), Brodersen P, Hansen EL, Kristensen HS (Departments of Infectious Diseases, Clinical Chemistry, and Anesthesiology, Blegdam's Hospital, Copenhagen, and from the Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark)

Twenty-one patients with acute pyogenic meningitis or acute encephalitis have been studied. The patients were hyperventilating spontaneously, the average \( \text{Pa}_2 \text{CO}_3 \) being 30 mm Hg. The investigations were carried out under general anesthesia (sodium pentobarbital, nitrous oxide, and d-tubocurarine) using artificial ventilation, and the \( \text{Pa}_2 \text{CO}_3 \) of each patient was maintained at approximately the same level as during spontaneous ventilation. Examination of the CSF (suboccipital) showed a marked lactic acid acidosis, ranging from 2 to 29 mmol/l (normal value about 1.3 mmol/l). Highest values were observed in patients with meningitis. The CSF pH was near normal in most cases. The regional cerebral blood flow (rCBF) was measured in all patients using the \(^{133}\text{Xenon} \) intracarotid injection technique. The rCBF showed varying degrees of reduction, the average value being 39 ml/100 gm per minute (normal value 50 ml/100 gm per minute). Marked differences were seen between the different groups of patients and in meningococcal meningitis the flow values were normal. The cerebral metabolic rate of oxygen (CMR \(_{\text{CO}_2} \)) was markedly reduced with an average value as low as 1.8 ml/100 gm per minute (normal value 3.3 ml/100 gm per minute). Highest, but still reduced, values were seen in meningococcal meningitis. The anesthesia could not account for the reduction in CMR \(_{\text{CO}_2} \). Based on other studies in our laboratory the anesthesia should reduce at the maximum the CMR \(_{\text{CO}_2} \) to 2.6 ml/100 gm per minute which is much higher than the average value of the patient studied, although in the range of values in patients with meningococcal meningitis. The jugular venous \( \text{P}_2 \text{O}_2 \) was markedly elevated in many cases, especially in patients with meningococcal and pneumococcal meningitis; values as high as 54 mm Hg (normal value 38 mm Hg) were observed. Thus clear-cut luxury perfusion with CBF surpassing the metabolic demand was observed in many cases. Cerebral vasomotor function was tested in all cases. Focal or global loss of autoregulation was observed in 14 of the 21 cases (normally the cerebral blood flow is independent of the arterial blood pressure within wide limits—so-called autoregulation). The reaction to changes of \( \text{Pa}_2 \text{CO}_3 \), however, was preserved—only lost in four of 17 patients.
tested (normally cerebral blood flow increases during hypercapnia and decreases during hypocapnia). Focal abnormalities of the rCBF or its regulation were infrequently seen in the patients with meningitis in contrast to the patients with encephalitis. Focal flow abnormalities thus were seen in three of 13 patients with meningitis but in five of seven patients with encephalitis. An additional patient with encephalitis suffered brain death and had stopped intracranial circulation.

X-71
Cerebral Blood Flow and Cerebral Metabolism in Patients With Chronic Acidotic Renal Insufficiency—Gottstein U, Held K (Chefarzt der Medizinischen Klinik des Bürgerhospitals, Frankfurt [Main], Germany)

In 24 patients with chronic renal insufficiency and uremia CBF was measured quantitatively by the N2O method, and cerebral metabolism analyzed with specific enzymatic techniques. At urea-N values of 142 mg % and arterial pH of 7.31, CBF was slightly elevated (63 ml/100 gm • minute), while CMRO2 (2.77 ml/100 gm • minute) and CMRglu (3.75 mg/100 gm • minute) were markedly reduced. The glucose-oxygen quotient (glucose A-V difference minus lactate and pyruvate A-V difference divided by oxygen A-V difference) declined to 1.13. By classifying the values into two groups, namely acidic (pH < 7.35) and nonacidic (pH > 7.35), different results were obtained:

(a) In 15 patients with acidic renal insufficiency, CBF was markedly elevated (69.0 ml/100 gm • minute). There was a significant negative correlation between pH and CBF: The lower the pH, the higher was CBF. CMRO2 and CMRglu and the glucose-oxygen quotient were significantly reduced.

(b) In nine patients with nonacidotic renal insufficiency, CBF was normal (52.9 ml/100 gm • minute), while again CMRO2 and CMRglu were reduced. In these patients, however, the decrease of CMRglu was distinctly smaller than in the acidic group. Therefore, the glucose-oxygen quotient did not differ significantly from normal.

There exists a significant positive correlation between pH and CMRO2 and CMRglu: The lower the pH the lower were CMRO2 and CMRglu. No correlation was found with urea-N levels.

X-72
The Relation Between Focal and rCBF Calculated by Bi-Compartmental Analysis and Initial Slope Index in Patients With Acute Brain Injuries—Cold G, Enevoldsen E, Jensen FT (The Neurosurgical and Radiophysical Departments, Arhus Kommunehospital, Arhus, Denmark)

A group of patients with mainly supratentorial injuries were subjected to repeated CBF studies during the first four to five days after the trauma. The CBF was calculated (1) on the basis of 15-minute 133Xenon clearance curves obtained by bi-compartmental analysis and (2) by a two-minute slope index. A 16-channel scintillation counter was used in the studies, which were performed under moderate sedation and relaxation and under artificial ventilation with moderate hypcapnia. Simultaneously, continuous measurements of intraventricular pressure and systemic arterial pressure as well as determinations of the end-expiratory CO2 were carried out. Arterial blood analyses comprised Pco2, Pao2, and pH.

During the same period, the patients were subjected to repeated neurological examinations. The focal operative findings and neurological manifestations were related to the rCBF as determined by the two methods.

Focal regions often revealed tissue peaks, a high f (g) and an abnormally low w(g).

Focal changes were most distinctly demonstrated by bi-compartmental analysis. In some cases, foci revealed by that method could not be traced by the initial slope index.

Regions with abnormal flow decreased in size on clinical improvement.

A focal region may manifest itself only by an abnormal w(g).

X-73
rCBF and Cerebral Vasomotor Response in Brain Tumors Following Dexamethasone Treatment—Hadjidimos A, Steingaard U, Fischer F, Reulen HJ, Weirauch D, Schürmann K (Department of Neurosurgery, University of Mainz, West Germany)

Hemispheric as well as regional CBF was found to be markedly reduced and vasomotor response severely damaged in patients with brain tumor. The reduction in local tissue flow may be attributed to an increased local tissue pressure due to increased local tissue water content as well as to increased intracranial pressure. Steroids have been shown to diminish perifocal brain edema and to improve the clinical status.

In the ongoing studies, ten patients with brain tumor were submitted to rCBF measurements (133Xe intra-arterial technique) before and six days after dexamethasone administration (24 mg daily). Vascular regulating mechanisms were investigated by functional tests (studies under neuroleptic analgesia, relaxation and controlled respiration).

At rest, before treatment mean hemispheric rCBF amounted to 28.3 ± 2.4 and increased to 34.9 ± 4.0 ml/100 gm • minute (n = 10) following dexamethasone treatment, i.e., an augmentation of 23.3%. In six cases rCBF increases ranging between 24% and 88%, with an average of 42%, were noticed. All patients of this group had (before treatment) a markedly reduced flow (25.6) and clinical symptoms of increased ICP. Three patients with an initially higher flow rate (35.9) revealed slight or no changes following treatment.

The beneficial effect of dexamethasone becomes even more striking when regarding the results of vasomotor response: In all ten cases the CO2 regulation and, in eight out of nine cases, the autoregulation were found to be remarkably improved.

The amelioration of the vasomotor response under treatment seems indicative of a restoration of the cerebrovascular tone which may be further related to changes in capillary permeability. Additionally, the removal of local brain edema with consequent decrease in local tissue pressure and increase in local tissue perfusion pressure may explain the obtained effect of dexamethasone on rCBF.
SYMPOSIUM ABSTRACTS

X-74

Clinical Usefulness of Regional Cerebral Circulation Studies With Sodium Pertechnetate—George RO, Larson SM, Mitchell TG, Natarajan TK, Preziosi TJ, Strauss HW, Udvarhelyi G, Wagner HN Jr (Johns Hopkins Hospital, Baltimore, Maryland)

Since the classic studies of Kety and Schmidt, clinical investigators have continued to search for a simple method to measure cerebral blood flow that would achieve the widespread clinical usefulness of techniques such as brain scanning. During the past four years, we have performed more than 1,200 studies of regional cerebral circulation in man using the scintillation camera and sodium pertechnetate. Our results indicate that useful information may be obtained in a significant number of patients in differentiating cerebrovascular disease from less serious neurological disease, and in the differential diagnosis of neoplasm, A-V malformation and cerebrovascular disease.

Initially, the method consisted of an intravenous bolus injection of 20 millicuries of technetium-99m pertechnetate, followed by vertex images recorded at two-second intervals. Inspection of the serial images revealed asymmetry in the time course of the passage of the tracer through the cerebral hemispheres in 50% of patients with acute cerebrovascular accidents, while none of those without cerebrovascular disease had asymmetry. Seventy-four percent of stroke patients with arteriographic abnormalities had abnormal patterns in the subjective study. In 22 patients with cerebral neoplasms, none had reduced cerebral circulation in the region of the lesion. Recently, a computer (PDP8) has been coupled to the camera to permit quantitative analysis of the data used to construct the images. This computer is initially used to correct field non-uniformities in the scintillation camera and allows some degree of spatial averaging. An observer then views the serial images with variable contrast enhancement and uses a light-pen to select areas of interest for further analysis. The computer indicates the time-course of activity in these selected regions.

A comparison was made in dogs of the cerebral time activity curves of 99m-Tc pertechnetate and microspheres labeled with 99m-Tc. The time-course of activity over the cranium of the dog was similar for both intravenous and left ventricular injections of sodium pertechnetate. The curves obtained with these agents were almost identical to those obtained when labeled microspheres were injected into the left ventricle. This similarity exists until the activity peak reaches its maximum.

We compared the areas under the time activity curves and the maximum count rates of two symmetrical regions of the brain in order to determine the ratio of regional perfusion in the two regions.

This method has now been applied in 104 persons including 50 normals. In the normal persons, flow ratios between symmetric head regions were 1.0 ± 1 (mean and standard deviation). Initial evaluation of 23 patients with cerebrovascular disease showed flow ratios in 17 greater than 2 SD from the mean of normals. In this group of patients, the site of the lesion determined by this method correlated well with the site suspected on clinical grounds. Validation of the method will require extensive study in many patients with a variety of abnormalities of cerebral perfusion. Our initial results in studies of regional cerebral circulation suggest that computer-assisted interpretation is of value as a supplement to the subjective analysis of serial images of the transit of sodium pertechnetate.

RESERVE

Changes of CBF and CSF in Brain Injuries—Seitz HD, Hirschauer M, Metzel E, Schrader H, Zimmermann WE (Department of Surgery, University of Freiburg, West Germany)

The purpose of this paper is to report on examinations of changes of the gas tension (P CO2), the appearance of different metabolites, of enzyme activities as well as changes of electrolyte and acid-base metabolism in cerebrospinal fluid (CSF) and the repercussions on the disturbance of cerebral blood flow (CBF) in brain injury (BI). We tried to find out if these changes permit conclusions as to prognosis and therapy.

Fifty patients with BI were divided into three groups according to the clinical severity of the injury. A group of ten normal human volunteers also was tested. Oxygen and CO2 tension, pH values, standard bicarbonate, base excess, lactate, pyruvate, electrolytes, and the enzymes LDH, GOT, GPT, CPK and ALD were tested in arterial and venous blood (A. femoralis and bulbis jugularis) within the first 12 to 24 hours after the injury. These examinations were repeated in one-day to two-day intervals. At the same time the cerebral blood flow was measured with a digital autofluoroscop and 133Xenon over 90 to 120 separate fields.

In severe cerebral trauma with coma and severe neurological and vegetative disturbances and a markedly pathological EEG we could show a strict correlation between gas-analytical, enzymatical and biochemical changes in CSF and the severity of the cerebral lesion going parallel with a distinct diminution of the CBF. Poor prognosis found its expression in the diminution of the O2 tension and markedly increased CO2 diminished bicarbonate level, elevated lactate level and a constant decrease of the pH-value as the result of a severe metabolic acidosis. In addition we found a marked increase of the enzyme activities and a diminution of the total blood circulation of more than 60%. At the same time a change of the relation of the separate compartments from 20:80% favoring the white substance was observed.

The severe metabolic acidosis in cerebrospinal fluid in BI cannot be influenced by the customary I. V. therapy, but by direct intrathecal administration of sodium bicarbonate. The results show marked improvement of the clinical situation in many cases with an improvement of consciousness, disappearing of the neurological disturbances, and normalization of the EEG changes. We also could show a marked increase of CBF after intrathecal sodium bicarbonate administration.

(1) The CSF changes of acid-base metabolism, O2 tension, enzymes and metabolites parallel the severity of a brain lesion after trauma and permit a prognosis as to further clinical development.

(2) The CBF examinations show a direct connection

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between the severity of the brain lesion, metabolic changes and the diminished cerebral blood flow.

(3) The therapy of metabolic acidosis in spinal fluid by intrathecal administration of sodium bicarbonate in cerebral injuries has a favorable influence on the cerebral blood flow and the brain metabolism.

SUMMARY: C. Fieschi

CO-CHAIRMAN: M. ROSSANDA
CHAIRMAN: G. McDOWALL

THURSDAY (2:00 TO 3:45 P.M.)

SYMPOSIUM ABSTRACTS

XI: Pharmacology and Anesthesia

XI-75 Effects of Systemic, Local and Cerebral Ventricular Prostaglandin F<sub>2α</sub> Administration on Canine Cerebral Circulation—Emerson T Jr, Radawski D, Veenendaal M, Daughtery R Jr (Departments of Physiology and Medicine, Michigan State University, East Lansing, Michigan 48823)

It has been proposed that prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) is responsible for the vasospasm associated with certain cerebral vascular problems (e.g., traumatic head injuries, subdural hemorrhage, etc.). The present study was undertaken to determine the influence of PGF<sub>2α</sub> on cerebral blood flow (CBF), cerebral vascular resistance (CVR), and cerebrospinal fluid pressure (CSFP). Aortic blood pressure (AP) also was monitored. CBF was measured from the cannulated sinus confluens after occlusion of the transverse sinuses. The effects of progressively faster infusion rates of PGF<sub>2α</sub> given systemically (50, 100, 200 μg per minute; n = 5), locally (20, 40, 80 μg per minute; n = 7), or into the right lateral cerebral ventricle (1, 2, 10, 100 μg/ml CSF; n = 7) were then determined. CSF outflow was via a needle in the cisterna magna. Average data ± standard errors from the CSF infusion are shown below (table).

Bilateral intra-carotid artery infusion of PGF<sub>2α</sub> caused a small fall in CBF at each level of infusion (max ± 8%), due to an increase in CVR (max ± 10%). AP and CSFP were unaltered. Systemic intra-aortic infusion of PGF<sub>2α</sub> caused no changes in the measured parameters except at the highest infusion rate (200 μg per minute) where CBF fell slightly (9%) and resistance rose moderately (14%). These data show that PGF<sub>2α</sub> can increase CVR, due apparently to active vasoconstriction and that the response depends upon the route of administration. However, the vasoconstriction produced by increasing the CSF concentration of PGF<sub>2α</sub> to enormous levels is: (1) minimal, (2) probably due to the autoregulatory phenomenon since AP increased, and (3) insufficient to decrease CBF. Therefore, these data do not support the hypothesis that PGF<sub>2α</sub> plays a major role in CBF regulation in normal or pathological states. (Supported in part by Michigan Heart Association and NIH Grant HL14774.)

XI-76 Inhibition and Reversal of Cerebral Vasospasm Induced by Prostaglandins—Yamamoto L, Feindel W, Wolfe L, Hodge C (Cone Laboratory for Neurosurgical Research and Donner Laboratory for Experimental Neurochemistry, Montreal Neurological Institute, McGill University, Montreal, Canada)

The mechanism of cerebral vasospasm associated with subarachnoid hemorrhage, intracranial lesions and migraine headache is unknown. In vasospasm related to subarachnoid hemorrhage, Kapp and others have demonstrated that an important vasoconstricting factor originated from the platelets and was not serotonin. Previously, we showed that prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and F<sub>2α</sub> (PGF<sub>2α</sub>) produced powerful and prolonged vasoconstriction of the small cerebral arteries. The potent vasoconstricting activity of PGE<sub>1</sub> was completely inhibited by a small amount of ethanol in the PGE<sub>1</sub> solution. Since prostaglandins are released from platelets as well as by stimulation of the cerebral cortex, we have examined them as factors in local regulation of cerebral blood flow and in the mechanism of cerebral vasospasm.

The present study was undertaken to see if ethanol infusion would release the cerebral vasospasm induced by PGE<sub>1</sub> in dogs and monkeys. Changes in cerebral hemodynamics at the microcirculatory level were observed directly on the exposed brains of animals during intracarotid infusion of PGE<sub>1</sub> and followed by intracarotid infusion of ethanol. The techniques used were: (1) 133Xenon clearance for measurement of rCBF, (2) fluorescein angiography, and (3) measurement of diameter changes in the epicerebral vessels.

The mean rCBF was significantly reduced by the initial intracarotid infusion of PGE<sub>1</sub> (1 μg per minute) from the control level of 0.549 ± 0.025 to 0.341 ± 0.027 (n = 16, P > 0.001) with mean reduction of 38%. The mean reduction of diameter of epicerebral vessels was 33% in less than 200 μ in diameter and 17% in the range of 200 to 500 μ. Fluorescein angiography showed no visible dye in the epicerebral vessels. After cerebral vasospasm was established by PGE<sub>1</sub> 0.5% ethanol in saline solution was infused into the carotid artery. The mean rCBF was then increased by 42% from 0.341 ± 0.029 to

### Table (XI-75)

<table>
<thead>
<tr>
<th>IR (ml/min)</th>
<th>Conc (ml)</th>
<th>AP (mm Hg)</th>
<th>CSFP (mm Hg)</th>
<th>CBF (ml/min)</th>
<th>CVR (PRU)</th>
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<td>0</td>
<td>0</td>
<td>134 ± 9</td>
<td>9.8 ± 1.3</td>
<td>20 ± 1</td>
<td>7.0 ± 0.6</td>
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<td>1</td>
<td>132 ± 7</td>
<td>11.5 ± 2.3</td>
<td>20 ± 3</td>
<td>7.0 ± 0.6</td>
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<tr>
<td>2</td>
<td>2</td>
<td>137 ± 6*</td>
<td>12.3 ± 3.0</td>
<td>20 ± 3</td>
<td>7.0 ± 0.6</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>142 ± 7*</td>
<td>11.8 ± 2.4</td>
<td>20 ± 3</td>
<td>7.6 ± 0.7*</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>150 ± 8*</td>
<td>12.2 ± 2.4*</td>
<td>21 ± 3</td>
<td>7.5 ± 0.6*</td>
</tr>
</tbody>
</table>

*= P < 0.05; IR = infusion rate; Conc = CSF concentration.
SYMPOSIUM ABSTRACTS

0.484 ± 0.028 (n = 16, P > 0.001). In addition, the vasoconstricted small epicerebral arteries dilated to control level and fluorescein angiograms appeared similar to the control studies. These studies suggest that prostaglandins may be involved in the genesis of vasospasm in man and that low concentrations of ethanol may be a means to prevent or relieve cerebral vasospasm.

XI-77

**Effect of Cyclic AMP on Regional Cerebral Blood Flow in Normal Baboons**—Hartmann A, Aoyagi M, Giri NY, Mathew NT, Meyer JS (Department of Neurology, Baylor College of Medicine, and the Baylor-Methodist Center for Cerebrovascular Research, Houston, Texas 77025)

When mammalian tissues were examined by other investigators, cerebral cortex was shown to have the highest capacity to produce cyclic AMP. It seemed reasonable to hypothesize that cyclic AMP plays an important role in cerebral function and possibly on the cerebral circulation. There is some evidence that cyclic AMP does influence cerebral circulation. Adenyl cyclase, the enzyme responsible for the conversion of ATP to cyclic AMP, has been reported to be associated with both alpha and beta adrenergic receptors which richly innervate the cerebral blood vessels. The potent cerebral vasodilator papaverine inhibits phosphodiesterase, resulting in an accumulation of cyclic AMP.

This hypothesis led us to measure the effect of intracarotid injection of N-6, 2′-O-dibutyryl cyclic AMP on cerebral blood flow. N-6, 2′-O-dibutyryl cyclic AMP was injected in 11 baboons and the regional cerebral blood flow was measured before and 30 minutes after administration using 183Xe and the gamma camera. Arterial P_{CO_2} and blood pressure also were recorded.

Nine measurements in seven monkeys with 5.0 mg per kilogram dibutyryl cyclic AMP showed significant reduction in rCBF with a mean reduction of 23.6%. The blood pressure was not significantly changed. Six dibutyryl cyclic AMP showed reduction of rCBF of similar to the control studies. These studies suggest that cyclic AMP does influence cerebral circulation. Adenyl cyclase, the enzyme responsible for the conversion of ATP to cyclic AMP, has been reported to be associated with both alpha and beta adrenergic receptors which richly innervate the cerebral blood vessels. The potent cerebral vasodilator papaverine inhibits phosphodiesterase, resulting in an accumulation of cyclic AMP.

XI-78

**Effects of Diphenylhydantoin on Local Cerebral Blood Flow**—DesRosiers M, Grave GD, Kuperberg HS, Kennedy C (National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke, Bethesda, Maryland 20014)

Diphenylhydantoin (DPH) has a variety of neuro-physiological and biochemical effects on the brain, but little is known of its action on the cerebral circulation. This has been investigated by measurements of local cerebral blood flow (LCBF) in rats with the 14C-antipyrine modification of the autoradiographical method. In a first series of studies DPH was infused intravenously over a 14-minute period in a dose of 50 mg per kilogram of body weight and allowed to equilibrate with brain over a two-hour period. At this time the mean plasma level was 15 μg per milliliter. In spite of a mild respiratory acidosis, mean values for LCBF were lower in all structures measured in the experimental animals than in those of the controls; a significant difference (P < 0.05) was attained in 13 of 22. The mean difference was −14%. The greatest changes were in the inferior colliculus (−25%), the auditory cortex (−22%), and the superior olives (−21%). A second series sought to detect any effect of DPH at much higher plasma levels (60 μg per milliliter) but long before saturation of DPH in brain. These conditions were attained by giving the same doses of DPH as were given in the first series but by shortening the infusion time to three minutes and by carrying out the LCBF procedure immediately following the infusion. In these studies no change in arterial pH or P_{CO_2} resulted. LCBF remained unchanged or was slightly higher in nearly all structures of the experimental animals compared to those in the controls. It is concluded that DPH acts to reduce LCBF variably in different structures of the brain and that this effect is probably secondary to a variable decrease in metabolic rate after its accumulation in brain.

XI-79

**Clinical Experience in the Management of Cerebral Vasospasm Using Intravenous Isoproterenol and Lidoaine Hydrochloride**—Sundt TM Jr, Onofrio BM (Cerebrovascular Clinical Research Center and the Department of Neurosurgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901)

Results in the treatment of cerebral vasospasm from subarachnoid hemorrhage with isoproterenol and lidocaine hydrochloride are summarized. The rationale for this form of treatment is presented along with pertinent clinical studies in vasospasm and cerebral blood flow measurements that preceded and formed a foundation for this form of management. It is hypothesized from experimental work available in the literature that in effect a subarachnoid hemorrhage produces an endogenous sympathectomy which sensitizes the receptor endings in the conducting vessels to circulating catecholamines and vasoconstrictive agents in the subarachnoid space. Stimulation of beta-adrenergic endings by intravenously administered isoproterenol could counteract spasm produced by stimulation of alpha-adrenergic endings from circulating catecholamines or blood breakdown products in the cerebrospinal
Barbiturate Protection Against Cerebral Infarction—Smith AL, Hoff JT, Nielson SL, Larson CP (University of California, San Francisco, and Stanford University, Palo Alto, California)

Anesthetics produce major alterations in cerebral blood flow and metabolism, but there is little basis for choosing an anesthetic agent for a patient undergoing a surgical procedure which is high risk. There is some evidence that some barbiturates inhibit cerebral vasodilation. The present study tests the hypothesis that pentobarbital produces cerebral protection against infarction produced by vascular occlusion. The protective effect could be related to decreased cerebral blood flow and intracranial pressure during barbiturate anesthesia or perhaps to decreased oxygen consumption. The data from the animal model may have relevance to clinical focal ischemia. We therefore compared the neurological and pathological sequelae of cerebral vascular occlusion in animals, produced during deep barbiturate, deeply halothane, and light halothane anesthesia. The right middle cerebral and internal carotid arteries were ligated in each of 14 dogs. Five dogs were anesthetized with 0.8% (end tidal) halothane and four dogs with 1.8% halothane. Anesthesia was induced in five additional dogs with pentobarbital 30 mg per kilogram, intravenously. Just before cerebral vessel clamping, the barbiturate dogs were given sufficient additional pentobarbital to reduce EEG frequency to less than one per second (mean total dose 55 mg per kilogram). Mean arterial blood pressure was maintained above 110 torr and P CO2 and P O2 were maintained normal. The animals were all allowed to awaken six hours after vessel ligation. Daily neurological examinations were performed for seven days postoperatively, at which time the animals were sacrificed. Gross and microscopic pathological examinations of the brain and quantitation of infarct lesions for reduction of hemorrhage. While preservation of cerebral cell substrate was demonstrated during normotensive anesthesia, glycolytic processes have not been studied during profound halothane-induced hypotension (HIH). Although normotensive inhalation anesthesia provides a degree of safety during cerebral ischemia, trimethaphan-induced hypotension (TIIH) and oligemic hypotension (OIIH) to a mean arterial pressure (MAP) of 30 mm Hg for 60 minutes have been shown to cause significant and marked elevations of cerebral tissue lactate concentration (CTLC). In the present study CTLC was determined in eight dogs as a measure of cellular conversion from aerobic to anaerobic cerebral metabolism during HIH was assessed to ascertain possible protective effects at 30 mm Hg MAP for periods up to an hour. In similar control dogs CTLC was determined at normotensive MAP. Mean CTLC after HIH at 5, 30, and 60 minutes were 4.34 (range 1.78 to 6.14), 5.92 (2.71 to 10.49), and 7.48 (3.37 to 12.86) mM per kilogram. Similar normotensive control figures were 4.54 (2.80 to 5.30), 4.51 (3.14 to 5.12) and 4.81 (3.32 to 5.92). Similar OH values were 7.18 (5.76 to 8.50), 14.42 (9.62 to 19.33), and 18.76 (16.85 to 22.30) mM per kilogram. During TIIH CTLC was 5.70 (4.18 to 8.06), 14.29 (13.25 to 16.14), and 13.81 (11.71 to 14.60) at 5, 30, and 60 minutes of MAP 30 mm Hg. There was no significant difference between HIH and control animals (P < 0.05) at any time. By five minutes in OH CTLC was significantly higher than HIH and controls (P < 0.05). At 30 minutes OH and TIIH were higher than controls (P < 0.01) and HIH (P < 0.01). By 60 minutes both OH and TIIH were significantly higher than control (P < 0.01, P < 0.01) and HIH (P < 0.01, P < 0.1) series. During systemic hypotension to 30 mm Hg MAP for 60 minutes HIH provides marked protection from cerebral ischemia compared to TIIH and OH. This is not due to selectively increased cerebral blood flow, since at these hypotensive levels cerebral vasodilatation is presumed maximal.

RESERVE

Effect of Anesthetic Depth on Cerebral Venous Oxygen Concentration—Smith AL (University of California, San Francisco, California)

Alterations in cerebral blood flow (CBF) and cerebral oxygen consumption (CMRO2) produced by the various inhalation anesthetics are not always related to anesthetic dose in any simple manner. However, previous work suggests that the ratio CBF/CMRO2 may be positively correlated with anesthetic dose, when the dose is expressed as multiples of the minimum alveolar concentration (MAC). (MAC is defined as the median...
SYMPOSIUM ABSTRACTS

anesthetic dose necessary to prevent movement in response to a painful stimulus; MAC multiple equals anesthetic concentration divided by minimum anesthetic concentration.) CBF/CMRO₂ is equal to the reciprocal of the cerebral arteriovenous oxygen content difference ([1/(A-V) O₂]; if arterial oxygen content is normal, 1/(A-V) O₂ is a function of cerebral venous oxygen tension PVO₂. It seemed possible that anesthetics might alter metabolic "control" of PVO₂. The present investigation attempted to further define the relationship between PVO₂ or (A-V)O₂ and anesthetic dose.

Three groups of six dogs each were studied. Normal arterial PVO₂, P A O₂, pH, and blood pressure were maintained. Animals in the first group were anesthetized with halothane concentrations of 0.1, 0.6, 1.3, 1.8, and 2.5 times MAC. Mean (A-V) O₂ was 9.8, 7.6, 6.5, 4.2, and 3.2 ml/100 ml, respectively, and mean PVO₂ was 37.0, 43.4, 48.5, 58.0, and 71.7 torr, respectively. Each dog in the second group was anesthetized with 0.7, 1.4, and 2.1 times MAC with enflurane; 0.7, 1.4, and 2.1 times MAC with halothane; and three mixtures of enflurane and halothane with MAC multiples of 1.4 or 2.1. PVO₂ values (±SE) were as follows:

<table>
<thead>
<tr>
<th>Total MAC multiple</th>
<th>0.7</th>
<th>1.4</th>
<th>2.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVO₂, halothane alone</td>
<td>42.9 ± 3.4</td>
<td>53.4 ± 3.4</td>
<td>59.2 ± 3.6</td>
</tr>
<tr>
<td>PVO₂, enflurane alone</td>
<td>42.2 ± 5.0</td>
<td>50.1 ± 4.3</td>
<td>61.4 ± 2.4</td>
</tr>
<tr>
<td>PVO₂, mixtures</td>
<td>48.9 ± 4.9</td>
<td>57.6 ± 5.3</td>
<td>57.4 ± 3.2</td>
</tr>
</tbody>
</table>

PVO₂ values increased significantly with anesthetic dose, but did not differ within dose levels. Thus PVO₂ and (A-V)O₂ depended on MAC multiple, but not on which agent or agents were given. Results in the third group of dogs, anesthetized with halothane and isoflurane, were similar to results in the second group.

The data suggest that PVO₂ and (A-V)O₂ are functions of MAC multiples, independent of which anesthetic is administered. A change in PVO₂ implies an alteration in cerebral circulatory control mechanisms. The data suggest that all inhalation anesthetics alter these control mechanisms in the same dose-related manner.

SUMMARY: G. McDowall

Session XII: CBF and Electrical Activity

THURSDAY (4:00 TO 5:45 P.M.)
CHAIRMAN: F. PLUM
CO-CHAIRMAN: T. SUNDT
XII-82
rCBF in Focal Cortical Epilepsy—Ingvar DH (Department of Clinical Neurophysiology, University Hospital, Lund, Sweden)

Twenty-three patients with epilepsy, mainly of focal cortical type, were studied. One patient had generalized serial epileptic attacks due to an intoxication. ¹³³Xenon measurements of rCBF with an eight-detector or 32-detector technique were carried out, usually in the interictal phase, but in a few patients during focal or generalized seizures. Interictally, in patients showing focal but nonparoxysmal abnormalities in the EEG, it was often found that the flow in the focal region was subnormal. Traumatic types of epilepsy often showed a diffuse flow reduction in the injured hemisphere. In patients with paroxysmal focal discharges in the EEG in the interictal phase, a mixed type of flow was found, most clearly in one patient with temporal lobe epilepsy studied with bilateral measurements. Over the region generating spike-sharp-wave activity peaked flow curves were recorded, indicating the presence of highly perfused compartments in the focal region. In the contralateral hemisphere where the EEG was normal, the flow values, as well as the clearance curves were normal. One patient with serial focal epileptic attacks in the right occipital pole, accompanied by transitory visual disturbances, showed a very marked increase of flow within the region of the epileptic discharge. The flow in the remainder of the ipsilateral hemisphere and on the contralateral side was normal. In the patient with serial generalized epileptic attacks a general cerebral hyperemia was demonstrated. Treatment with general anesthesia blocked the paroxysmal discharges and gave a marked flow reduction. In this case, records of the intracranial pressure showed that each epileptic attack in addition to the increased flow was accompanied by an increase of the intracranial pressure.

The epileptogenic focus, which anatomically often shows gliosis and a reduced number of neurons as well as a reduced capillary bed, was found to have a subnormal blood flow in the interictal phase. During ongoing paroxysmal discharge, the flow in the epileptogenic focus may increase and mixed flow curves are recorded which demonstrate the presence of highly perfused tissue compartments. During fully developed epileptic seizures of focal or generalized type, very high blood flows were recorded over discharging regions. These findings agree with numerous recent investigations on the pathophysiology of the epileptic seizure. It appears likely that neuronal anoxia-hypoxia during the synchronized epileptic discharge may cause tissue lactacidosis which leads to hyperemia. Possibly the consequences of neuronal anoxia-hypoxia also may play a role for the propagation of the focal discharges.
Correlated poorly with direct biochemical measurements of lactate and the lactate pyruvate ratio occurred early in the seizure, and persisted into the postictal period. Estimates of surface pH changes by electrodes showed no evidence of increased lactic acid production whereas an increased arterial blood pressure and a metabolic acidosis were observed, while the MABP increased only 20%. The CBF increase lasted two to three minutes after the seizures. A postictal (A-V)O₂ decrease to about 50% lasting three to five minutes indicated relative hyperemia and postictal CMRO₂ depression. At 15 minutes CBF and (A-V)O₂ were back to resting level. During seizures jugular venous P₂O₅ and P₀₂ increased both about 10 mm Hg and the average RQ increased from 0.95 to 1.29, followed by a postictal depression to 0.61 before it approached unity. The A-V lactate difference increased in average by 0.08 mmol per liter (P = 0.06).

Recent studies by Plum, Posner and coworkers showed a 30% to 50% increase of local cortical blood flow during seizures whereas an increased arterial blood pressure and impaired autoregulation were demonstrated. The striking RQ increase and the small increase in jugular venous lactate as observed in the present study suggest production of fixed acid (lactic acid) within the brain during seizures, even when arterial hypoxemia was avoided. It is concluded that the mechanism by which CBF increases during seizures probably involves both a rise in arterial blood pressure and a metabolic acidosis causing vasodilation and impaired autoregulation.

Eleven patients with endogenous depression treated with electroconvulsive therapy (ECT) were studied while they were pentobarbital-anesthetized, paralyzed and ventilated with either 33% or 100% oxygen. CBF was measured by the intra-arterial ¹³¹ Xenon method.

Artificial differences for oxygen, CO₂, lactate and glucose were determined. Mean arterial blood pressure was monitored in two patients. CBF was calculated as CBF₀.₅₅₅tep-

The resting CBF and CMRO₂ levels due to the anesthesia were 30% to 40% below the normal values for awake man. During seizures an increase in CBF, CMRO₂, and CMRGlucose of about 100% was observed, while the MABP increased only 20%. The CBF increase lasted two to three minutes after the seizures. A postictal (A-V)O₂ decrease to about 50% lasting three to five minutes indicated relative hyperemia and postictal CMRO₂ depression. At 15 minutes CBF and (A-V)O₂ were back to resting level. During seizures jugular venous P₂O₅ and P₀₂ increased both about 10 mm Hg and the average RQ increased from 0.95 to 1.29, followed by a postictal depression to 0.61 before it approached unity. The A-V lactate difference increased in average by 0.08 mmol per liter (P = 0.06).

Recent studies by Plum, Posner and coworkers showed a 30% to 50% increase of local cortical blood flow during seizures whereas an increased arterial blood pressure and impaired autoregulation were demonstrated. The striking RQ increase and the small increase in jugular venous lactate as observed in the present study suggest production of fixed acid (lactic acid) within the brain during seizures, even when arterial hypoxemia was avoided. It is concluded that the mechanism by which CBF increases during seizures probably involves both a rise in arterial blood pressure and a metabolic acidosis causing vasodilation and impaired autoregulation.

XII-84 Alterations in Cerebral Energy Metabolism, Brain pH and Cerebral Blood Flow During Indoklon-Induced Seizures in the Cat—Howse D, Caronna J, Duffy T, Plum F (Cornell University Medical College, New York, New York)

A correlation between alterations in brain energy metabolism, acid-base status, cerebral blood flow, and blood gases during experimental seizures was carried out in paralyzed ventilated cats. Bilateral burr holes exposed parietal cortex which was bathed in mock CSF held in an acrylic well. Brain surface pH was recorded continuously by a glass electrode. At six points following seizure induction by hexafluorodiethyl ether, brain tissue was frozen in situ by liquid N₂ and used for biochemical assay, immediately after drawing arterial and superior sagittal sinus blood samples.

Brain energy state declined during the seizure but recovered within 30 seconds. Major increases in brain lactate and the lactate pyruvate ratio occurred early in the seizure, and persisted into the postictal period. Estimates of surface pH changes by electrodes correlated poorly with direct biochemical measurements of the simultaneously frozen tissue. The cerebral lactacidosis and increased L/P ratio occurred at a time when superior sagittal sinus P₀₂ and BP were markedly elevated, implying increased reduction of the cytoplasmic redox state at a time of increased oxygen availability. Estimates of tissue pH indicated an acid shift early in the seizure which persisted into the postictal period, with a time course that paralleled the duration of loss of autoregulation that followed seizures in comparably treated animals.

All the findings are compatible with the concept that cerebral vascular resistance during states of increased cerebral blood flow and EEG was studied in anesthetized cats. Starting with a gas mixture of 25% O₂ and 75% N₂ the animals were ventilated mechanically. Hypercapnia was induced by adding 6% or 12% CO₂. The oxygen content was maintained at 25%. At intervals of 30 minutes the respective gas mixtures were changed. At three-minute intervals blood flow was determined by means of the local application of hydrogen. Simultaneously, the fronto-occipital EEG was recorded. The EEG information was Fourier-analyzed and the integral over the frequency range of 8 to 13 per second (α-power), 14 to 49 per second (β-power) and 1 to 49 per second (total power) was calculated. Changes of the mean brain diameter were taken as a measure of brain volume changes.

Under normocapnic conditions (Paco₂ about 25 mm Hg) the mean values of cortical microflow were 2 μl·min⁻¹·g⁻¹. The administration of 6% CO₂ (Paco₂ about 45 mm Hg) yielded a 50% increase of local cortical blood flow, as the transformed EEG showed a 30% to 50% increase of α, β, and total power. During ventilation with 12% CO₂ (Paco₂ about 75 mm Hg) cortical microflow reached twofold to threefold of the respective initial values. At the same time the power analysis of the bioelectrical activity showed a 30% to 50% decrease in the above-mentioned frequency ranges. These effects were reversible with a latency of some minutes. In 20% of the experiments with application of 12% CO₂ cortical microflow initially increased, then decreased to microflow values in normocapnia. In these cases Fourier analysis of EEG showed in all frequency ranges a marked decrease beneath the normocapnic values (in some experiments to 30%).

The cerebral hyperperfusion under hypercapnic, normoxic conditions is therefore hardly able to sustain the energy metabolism of the brain. Whether this critical supply condition is due to a metabolic impairment or to a possible hyperperfusion of deeper cortical structures which are not detected by the applied
flow method (e.g., shunt-perfusion) is a question of further investigation.

XII-86
The Time Course of the Cerebral Circulatory Response to Metabolic Depression—Keaney NP, McDowall DG, Pickerodt VWA, Turner JM, Lane JR, Coroneos NJ (Department of Anesthesia, University of Leeds, Leeds, England)

The relationship between CBF, cerebral metabolism, EEG and certain brain stem centers is not clearly established. For the discussion of the metabolic and neurogenic control theories the time between cerebral metabolic depression and CBF decrease is important. A search of the literature yielded no information apart from some work with barbiturates by Ingvar et al. (1962) who state that their results could not be used to define this time relationship because of BP depression. We used althesin (a new steroid intravenous anesthetic agent) to study the time course of cerebral circulatory responses to cerebral metabolic depression as we had already shown that althesin reduced CBF and cerebral oxygen uptake with little disturbance of blood pressure.

Four baboons anesthetized with N2O/O2 and halothane (0.5%) and artificially ventilated to normocapnia received central venous injections of althesin (0.05 ml per kilogram) mixed with technetium 99m so that the arrival of the drug bolus in the brain (DBA) could be timed by a gamma detector. Mean blood pressure (MBP) and internal carotid blood flow (CarBF) were measured electronically continuously and carotid vascular resistance (CVR) calculated. The EEG was recorded and the times after althesin injection of initial and peak DBA, of MBP fall, of EEG slowing, of CarBF decrease and of CVR rise were noted.

The results (means ± SEM) are as follows:

<table>
<thead>
<tr>
<th>Event</th>
<th>Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBA</td>
<td>5.4 ± 0.2</td>
</tr>
<tr>
<td>DBA (peak)</td>
<td>7.6 ± 0.3</td>
</tr>
<tr>
<td>MBP fall</td>
<td>8.2 ± 0.4</td>
</tr>
<tr>
<td>EEG slowing</td>
<td>9.1 ± 0.4</td>
</tr>
<tr>
<td>CarBF decrease</td>
<td>10.9 ± 0.4</td>
</tr>
<tr>
<td>CVR rise</td>
<td>11.8 ± 0.3</td>
</tr>
</tbody>
</table>

Paired results showed that (1) the difference between DBA (peak) and EEG slowing was 1.2 ± 0.9 seconds and was not significantly different from zero; thus, the EEG change was almost instantaneous with tissue arrival; and (2) the CVR rise occurred 4.0 ± 0.5 seconds after DBA (peak) (P < 0.001). This is the maximum time for the response. CarBF began to decrease about one second earlier but this may have been passive. The MBP fall at the time CVR began to rise was 6.8 ± 0.7 mm Hg and MBP continued to fall but CVR continued to increase. The four seconds between drug arrival and vascular constriction agrees with the findings of Wahl et al. (1970), who showed that vasodilatation started five seconds after the micropuncture application to pial arterioles of mock CSF containing no bicarbonate.

Calculations based on the cortical “CO2 dissociation curve” of Siesjo (1962) and on the CMRO2 decrease we previously measured show that the maximum tissue

P O2 fall was less than 0.5 mm Hg in the four seconds to cerebral vasoconstriction.

XII-87
The Time Course of the Cerebral Circulatory Response to Metabolic Depression—Keaney NP, McDowall DG, tory of Circulatory Research and Laboratory of Clinical Neurophysiology, Rigshospitalet, Copenhagen, Den-

In 80 patients operated on for stenosis of the carotid artery manual EEG frequency analysis was related to changes in rCBF and internal carotid artery pressure before and during a two-minute test occlusion of the carotid artery. Halothane-N2O-O2 was used for anesthe-

rCBF was measured by the 133Xe intra-arterial injection method with 16 external scintillation detectors.

Changes in the EEG during the test occlusion occurred in 20 patients. There was no interindividual or intraindividual relation between rCBF and EEG. rCBF could be reduced by more than 30% without EEG changes.

When the rCBF was reduced to 16 to 22 ml/100 gm per minute, there was slowing of the EEG. When rCBF was reduced to 11 to 19 ml/100 gm per minute, there was flattening of the EEG.

When EEG changes occurred, the internal carotid artery pressure in the stump averaged 35 mm Hg (15 to 50 mm Hg). In the remaining patients stump pressure averaged 70 mm Hg (36 to 113 mm Hg).

The results indicate that rCBF values of 16 to 22 ml/100 gm per minute are critical for maintenance of adequate cerebral metabolism during general anesthesia. Further, stump pressures in the internal carotid artery below 50 mm Hg are associated with inadequate brain perfusion.

XII-88
Altered Cerebral Metabolism and Blood Flow in Response to Physiological Stimulation—Salford LG, Duffy TE, Plum F (Department of Neurology, Cornell University Medical College, New York, New York)

During the increased metabolic activity of epileptic seizures, CBF rises while cerebral CO2 production exceeds oxygen consumption. Contrary to our earlier findings, we now find that this alteration in RQ is consistently associated with a lactate rise in the tissue providing strong evidence for a close coupling of flow to metabolism in seizures. The present experiment examined the flow-metabolism couple under circumstances more closely resembling physiological stimulation of the brain.

Male Wistar rats were artificially ventilated, lightly anesthetized with N2O and paralyzed with tubocurarine. One sciatic nerve was isolated and stimulated (10 V, 0.2 msec, 1/sec X 30 or X 300). EEG, cerebral evoked response and cerebral A-V differences for O2 and CO2 were measured. CBF was estimated by heat clearance techniques. At set points during stimulation brains of comparably stimulated animals and controls were frozen for lactate analysis.

During sciatic stimulation, an evoked response was recorded over both hemispheres with its maximum in the contralateral sensorimotor cortex, a finding compa-
rable to the response in man. Blood pressure did not consistently change. CBF increased, A-V differences for oxygen content narrowed, cerebral venous oxygen tension rose, while calculated A-V CO₂ differences remained relatively unchanged. Brain lactate rose from 1.80 mM per liter (control) to 2.88 mM per liter (P < 0.01) in the contralateral hemisphere and to 2.54 (P < 0.05) in the ipsilateral hemisphere. Blood lactate did not change.

The findings imply that increased cerebral stimulation increases lactate production despite an abundantly available oxygen supply. The accompanying rise in CBF is best explained as reflecting the fall in tissue pH rather than any direct neurogenic influence on the vascular wall.

RESERVE
The Relationship Between CBF and EEG (Alpha/[Delta + Theta] Ratio) During Photic Stimulation in the Rabbit—
De Valois JC, de Blecourt CV (Dutch Central Institute for Brain Research, IJdijk 28, Amsterdam)

The aim of this investigation was to find correlations between electrical activity of the brain and the blood flow in localized brain areas. The blood flow was measured with 133Xenon. To calculate the blood flow through the cortical layers two-compartmental analysis of the clearance curves was performed together with the determination of the initial slope indices. The brain area chosen for this investigation was the optic cortex. The electrical activity of the occipital cortex can easily be changed by photic stimulation of the retina. CBF can be measured in this area by using proper collimation. The EEG was recorded with four silver/silver chloride electrodes implanted in the skull overlaying the optic cortex on both sides. Light stimulation of the retinas of both eyes was accomplished by two identical light guides of glass fibers connected to a stroboscope. The light guides were mounted in dark plastic cups placed on the eyes. The EEGs were analyzed with a filterset in the classic EEG frequency bands using an analysis epoch of 30 seconds. The mean amplitude in each frequency band was measured and the ratio of alpha/(delta + theta) turned out to be a useful parameter to describe the EEG in quantitative terms. In a series of experiments consisting of 18 animals multiple EEG/CBF measurements were performed. In each animal at least one EEG was recorded without photic stimulation and the other measurements took place with stimulation frequencies of 2, 4, 8, 16, and 32 cycles per second, randomly distributed in each animal to prevent any bias. In each animal at least six combined observations were made.

With stimulation frequencies ranging from four to 16 cps the flow is proportional to the flash frequency. At higher stimulation frequencies the EEG is no longer being “driven” and this relation is lost. The EEG parameter correlates very well with the flow values in this frequency domain, with a spearman correlation coefficient of 0.92.

SUMMARY: F. Plum
A brief bolus injection of 10 mCi $^{133}$Xenon dissolved in 0.5 cc is washed into any convenient vein. The gamma activity is counted and recorded on tape over frontal and posterior parietal regions with 1" diameter collimated scintillation detectors, and also in the end-expired air. The latter forms a reasonable approximation to the arterial concentration. The Fick equation is assumed to hold for each of three compartments; average gray matter, white matter, and extracerebral. Deconvolution of the head curves is accomplished by solving the Fick equation separately for each compartment by individually projecting them down onto an inkwriter recording of the head curves.

First, the extracerebral component is fitted to the curves by assuming that after 25' the white matter flow has virtually disappeared. After 10' it is assumed that the gray matter flow is insignificant, and that the curve therefore consists of white matter plus extracerebral, and is fitted by adding on the white matter component.

Finally, the curve is completed by adding on the initial gray matter component. The analog computer fit has been tested on machine-generated curves by using the convolution integral and known flow values. The accuracy based on the average of ten fits per curve is better than 4%.

The sensitivity of the end-expired air curve was tested by varying the cret plateau, falling slope, and final decay rate and measuring the effect on cerebral blood flow. The flow values were most sensitive to the final decay rate. The technique is not suitable for patients with severe pulmonary disease or respiratory irregularity, and preliminary studies confirm the sensitivity of the method to changes in $P_{\text{a}}O_2$.

Flow values on ten normal patients between the ages of 21 and 56 years of age are: $F_g = 75 \pm 9$ ml/100 gm; $F_w = 24 \pm 2$ ml/100 gm.

XIII-91

An Evaluation of the Xenon Inhalation Technique for the Measurement of Cerebral Blood Flow—Corbett JL, Edelman BH (Department of Neurology, Churchill Hospital, Oxford)

The $^{133}$Xenon inhalation technique has undergone a number of modifications since it was first described by Mallett and Veall in 1963. The most recent modifications are the gamma ray subtraction technique and the simplified procedure for determining flow in gray matter. The noninvasive nature and relative simplicity of data analysis make both methods highly attractive. The main objection to these procedures is extracranial contamination. While these newer methods minimize gamma emissions from this source, there is no practical way in which activity from these tissues can be entirely eliminated. The work of Obrist has shown a good correlation between gray flow measured by the inhalation technique and intracarotid injection of $^{133}$Xenon, but no data are available for similar studies using the gamma subtraction technique.

There have been no reports of simultaneous measurement of cerebral flow by $^{133}$Xenon inhalation and other methods. While the error arising from extracranial contamination is reported to be small, it is important to know whether this is likely to influence measurements of cerebral flow in conditions such as hyperventilation and drug administration where independent changes in flow of the noncerebral tissues are expected.

In order to evaluate these problems a series of cerebral blood flow studies was carried out on volunteer subjects. Cerebral blood flow was measured using the Xenon inhalation technique while simultaneous measurements of cerebral arteriovenous oxygen differences were made. Studies were carried out at rest, during hyperventilation and while an alpha blocking drug (thymoxamine) was infused. Data from the Xenon inhalation studies were analyzed according to the method described by Obrist and also were subjected to spectrum subtraction analysis.

The changes in cerebral blood flow recorded with the Xenon inhalation technique paralleled those measured using cerebral A-V oxygen content differences, and there was a good correlation between percentage decrease in cerebral blood flow with hyperventilation as measured by both methods. The Xenon inhalation study revealed no significant differences between the two methods of data analysis.

These findings confirm the usefulness of the atraumatic Xenon inhalation technique in providing a measure of cerebral blood flow under resting conditions, during hyperventilation and with administration of pharmacological agents.

XIII-92

The $^{133}$Xenon Inhalation Method: Assessment of rCBF in Carotid Endarterectomy—Obrist WD, Silver D, Wilkinson WE, Harel D, Heyman A, Wang HS (Duke University Medical Center, Durham, North Carolina)

One advantage of the noninvasive $^{133}$Xe inhalation method is the opportunity to acquire adequate normal control data that can serve as a baseline for interpretation of patient findings. Another advantage is the ability to perform serial bilateral studies, thus making it possible to assess changes in cerebral blood flow related to the natural history of a disorder or to therapeutic intervention. Fast compartment (gray matter) rCBFs were obtained by a previously described method in 30 young control subjects, 25 normal elderly volunteers, and 12 patients undergoing carotid endarterectomy. The procedure involved extracranial monitoring of a 10-minute clearance curve, following one minute of $^{133}$Xe inhalation. A two-compartment deconvolution was performed, using end-tidal air as an estimate of arterial input. Eight regional detectors (15 mm diameter) were employed; four over each hemisphere, except that in some patients six probes were placed on the affected side. Blood flow values were corrected for arterial $P_{\text{a}}O_2$ estimated capnographically.

Statistical analysis of the young and elderly control data revealed a high correlation ($r = +0.94$) between homologous regions of the two hemispheres. Blood flow differences between sides of 8% or more occurred less than once in 20 times. Test-retest correlations, however, were not as high ($r = +0.80$) due to a large day-to-day variability. For a given region, a difference of 15% or more between two days was required in order to infer a change at the 0.05 level of significance.

Using the control data as a basis for interpreting patient results, an assessment was made of rCBF...
changes associated with carotid endarterectomy. Cerebral blood flows were obtained preoperatively and, again, five days postoperatively. Significant increases were found in nine of the 12 patients; two showed no change; one had a decrease in flow. Four of the nine patients with increases revealed greater changes in the hemisphere ipsilateral to the surgery; the remaining had bilaterally symmetrical increases. Anterior and central probes showed greater changes than posterior placements. These 12 patients are now being followed after a three-month postoperative interval. Additional patients are currently being added to the series.

XIII-93
Variability of Repeated Clinical Measurements of Cerebral Blood Flow—Miller JD, Wyper D, Fitch W, Rowan JO, Grossart KW, Garibi J, Pickard JD (M.R.C. Group for Research into the Cerebral Circulation [Jennett WB, Harper AM], Institute of Neurological Sciences and Regional Department of Clinical and Bio-engineering, Glasgow, Scotland)

The significance of induced changes of CBF depends largely on knowledge of the random variation in CBF which occurs when no deliberate flow alteration is induced. This information should be known not only for “normal patients” but also for those in any group likely to be studied; variation also must be established over the full duration of any proposed study.

By injection of $^{133}$Xe solution into the internal artery (ICA), four successive measurements of CBF in the frontal, temporal and parietal regions were made in 12 anesthetized, ventilated patients in whom blood pressure, arterial P$_{\text{O}_2}$ and body temperature were held constant throughout the study. The same protocol was used in 20 patients, but using common carotid artery (CCA) injections of $^{133}$Xe. In a further 12 patients, ICA and CCA injections were compared in each study, and in ten additional patients the effects of carotid angiography on CBF were measured at 20 and 40 minutes from the injection of contrast. Correlations were made between CBF estimated from H/A extrapolated to infinity and by the initial slope (IS) method, and in those patients in whom bi-compartmental analysis was possible, there was an excellent correlation between weighted mean CBF and H/A flow, the regression equation being:

$$\text{CBF} (\text{w. mean}) = 1.14 \text{CBF} (\text{H/A}) + 1.1 \text{ml/100 gm per minute}$$

and the 90% confidence limits were ±14%.

In comparing ICA and CCA injections, the mean difference of 3 ml/100 gm per minute and the individual differences were well within the expected random variation. When CBF before angiography (46.4 ml/100 gm per minute) and after angiography (45.6 ml/100 gm per minute) were compared, there was no significant difference even on paired $t$ testing at 20 or at 40 minutes.

There was good correlation between H/A and IS measurements of CBF, with the regression equation:

$$\text{CBF (IS)} = 1.37 \text{CBF (H/A)} - 9.7 \text{ml/100 gm per minute}; r = 0.94, P << 0.001.$$
SYMPOSIUM ABSTRACTS

placed over the opened cranium. Xe was injected in the a. carotis communis via a thin catheter. Experiments were done with open and closed a. carotis externa. Occlusions were checked by angiograms. An amount of 65% of the 81-kev gamma rays of \(^{133}\text{Xe}\) is converted to 31-kev roentgen rays. The different energy levels were separated by pulse-height-analyzers. The decay-curves of both were registered during clearance.

The decay of the "31-kev-curve" is faster than the decay of the "81-kev-curve." This is in agreement with the anatomic configuration: a highly perfused cerebral cortex and a less perfused inner part of the cerebrum. The ratio of the intensities of 31-kev and 81-kev radiation (corrected for background) is used as an index for localization of an "equivalent place source" during clearance.

With a digital computer the 81-kev and 31-kev decay-curves were analyzed in a sum of two exponentials and a constant. A fitting procedure according to Marquardt's principle has been used. The exponents of corresponding exponentials turned out to differ significantly. This cannot be caused by proportional contributions of scattered 81-kev gamma rays in the energy region of 31-kev. Similar measurements were performed in vitro on a model of two compartments for comparison.

The discrepancies might disappear, if a model of more than two exponentials was assumed. The curves, therefore, were analyzed also in three exponentials. It will be shown that these results, however, are very unreliable because of non-orthogonality properties, which are mathematically inherent to exponentials. A preliminary conclusion is that the figures found with a model of two compartments for cerebral blood flow studies are affected by the energy of the radiation when low energy radiation is used.

XIII-96
A Method and Instrumentation for Quantitating Local Cerebral Blood Flow in 144 Subdivisions of Human Brain, Using \(^{133}\text{Xe}\) and a Germanium Detector Array—Barker J, Youdin M, Reich T (Goldman Cerebrovascular Laboratory, Institute of Rehabilitation Medicine, New York University School of Medicine, New York, New York 10016)

Local cerebral blood flow is defined as the flow in each of 144 cubic subdivisions throughout the brain, a three-dimensional localization not achieved by previous methods. It is measured by (a) highly selected multilinar, multidetector observations of uptake or washout phases of \(^{133}\text{Xe}\) exchange, (b) computer resolution of local concentration changes from these specific regional measurements, followed by (c) flow calculations based upon local concentration changes as a function of time. Resolution of heterogeneous local concentrations within the brain mass is the most difficult aspect. It requires solution of multiple simultaneous linear equations in subsets of 36 for each brain quadrant, each equation representing a unique contribution of information obtained by choosing specific angulations and collimations for viewing 81 kev emissions. One equation for each detector considers detector efficiency, geometry, collimator factors, tissue attenuation, inverse square of distance effect, and the variations in some of these due to individual head size. Smaller subsets measured at 31 kev contribute to the accuracy. New instrumentation was designed to meet these requirements and the additional one for highly discrete energy resolution at 31 and 81 kev. New ultrapure germanium crystals met the latter requirement but had not been incorporated in arrays. The 36-detector module which we have constructed and which is sufficient for analysis of each brain quadrant independently is the first multidetector solid-state array, an advance in nuclear technology attributable to our need in this problem for discrete energy resolution, excellent stability, low background, and small detector size suitable for packing 144 detectors into the limited space about the head. A system for handling large masses of digital data during rapid transients also was required and solved by use of a minicomputer interfaced to scan outputs of energy analyzers directly and to accumulate as a programmed function of time.

Our instrumentation has been designed specifically for utilization of the one-minute uptake method, using respiratory administration and end-tidal sampling to assess arterial concentration changes, with the intent to provide a rapid atraumatic procedure suitable for scanning large populations as well as a result-return time of minutes.

(Supported by the H. Goldman Foundation and in collaboration with General Electric Company Space Technology Division.)

XIII-97
A 256 Detector System for Measuring Regional Cerebral Blood Flow—Sveinsdottir E, Lassen NA (Department of Computer Science, University of Copenhagen, and the Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen, Denmark)

A dynamic gamma camera has been constructed based on 256 scintillation crystals, each crystal being coupled via a light guide to one photomultiplier. The system allows recording of \(10^6\) counts per second with a counting loss in the order of 2%, a performance which is far better than that of other comparable systems, as the single crystal camera (Anger), the image intensifier camera and even the multi-crystal-coincidence counting (Render and Blau) camera.

The 256 detector system is coupled on-line to a small computer and the results are obtained with practically no delay on an oscilloscope and on a color TV. Cerebral blood flow levels are depicted in analog manner using a color scale or a gray tone scale. The system also is used for making conventional static images of blood-brain-barrier abnormalities ("brain scans").

The system is designed with particular emphasis on detecting and locating minor alterations in cerebral circulation as associated with intracranial disease or with physiological alterations of brain function associated with mental function. The preliminary results obtained by a comparison of these high resolution cerebral blood flow studies to conventional neuroradiological techniques will be described.
Diurnal Rhythm in Cerebral Blood Volume of Mice—Owman CH, Edvinsson L, Nielsen KC (Department of Histology and Neurosurgical Clinic A, University of Lund, Lund, Sweden)

The brain vascular system receives its sympathetic nerve supply from the superior cervical ganglia, which are unique in that they receive direct information about environmental light via well-known pathways: a diurnal rhythm controlled by light has been demonstrated for norepinephrine in the rat pineal and submaxillary glands. Against this background, cerebral blood volume in mice was determined around the clock after having maintained the animals for two weeks in 12 hours of light/12 hours of darkness.

A radioisotope dilution technique was used: RIHSA was injected into the tail vein of mice and, after proper mixing time (10 minutes), the circulation was stopped by immersion of the whole animal into liquid nitrogen (−196°C). The brain was weighed and placed in a plastic tube, 25 μl blood was drawn from the heart (internal standard) and collected in another tube, after which radioactivity was measured in an autogamma spectrometer.

The CBV around noon corresponded with values previously presented (35 to 40 μl per gram). Later on, values were significantly reduced to a minimum at 4 p.m. A low CBV was then maintained during the following eight hours, after which there was an increase to a maximum blood volume near daybreak. The difference between peak and trough was statistically significant. CBV then returned to the somewhat lower level mentioned for midday.

CBV measured at noon in animals kept in constant darkness for two weeks was significantly higher than time-matched controls on the light/darkness schedule, whereas animals in two weeks of constant light had similar CBV as the control animals.

It is notable that the pattern of 24-hour variation in CBV resembles that of the norepinephrine rhythm in the pineal and salivary glands, which would favor the assumption that CBV is affected via a sympathetic neural reflex mechanism influenced by environmental light.

SUMMARY: D. Ingvar

Session XIV: Neurogenic Control I

FRIDAY (11:00 A.M. TO 12:45 P.M.)

CHAIRMAN: P. SCHEINBERG

CO-CHAIRMAN: E. SKINHOJ

XIV-98

The Effect of Alpha-Adrenergic Blockade on the Response of the Cerebral Circulation to Hypocapnia—Hoff JT (Visiting Fellow from the Department of Neurological Surgery, University of California, San Francisco), Harper M, Sengupta D, Jennett B (M.R.C. Cerebral Circulation Research Group at the Wellcome Surgical Research Institute and the Institute of Neurological Sciences, The University of Glasgow, Glasgow, Scotland)

It has recently been reported that the hypocapnic reduction in CBF is partially or completely abolished when the sympathetic system is blocked with Thymoxamine. This observation led us to explore the effect of alpha blocking agents on the CBF during hypocapnia in baboons.

Adult baboons were anesthetized with Phencyclidine, N₂O and oxygen with intermittent positive pressure ventilation. Pa_CO₂, Pa_O₂ and pH were measured on the micro-Astrup system. Blood pressure was measured from a catheter in the femoral artery. CBF was measured from the clearance of ¹³³Xe following its injection into the lingual artery, the remaining branches of the external carotid artery being tied. The scalp and temporal muscles were removed on the side of CBF measurement.

In one series of experiments, in four animals, the intravenous infusion of Thymoxamine (1.33 mg per kilogram per hour) failed to alter the hypocapnic CBF response. At normocapnia (Pa_CO₂ 41 mm Hg) the CBF was 57 ml/100 gm per minute. During hypocapnia (Pa_CO₂ 22 mm Hg) the CBF fell to 39 ml/100 gm per minute. During hypocapnia + Thymoxamine (Pa_CO₂ 21 mm Hg) the CBF remained low at 38 ml/100 gm per minute. During the infusion of Thymoxamine, the MABP fell from 97 to 85 mm Hg.

In a second series of experiments, in four animals, the intravenous injection of Phenoxylbenzamine (1.5 mg per kilogram) failed to alter the hypocapnic CBF response. The figures were (a) control—CBF 44 at Pa_CO₂ of 40, (b) hypocapnia—CBF 32 at Pa_CO₂ of 21, (c) hypocapnia + Phenoxylbenzamine—CBF 33 at Pa_CO₂ of 19. The MABP fell from 99 to 87 mm Hg during the infusion of Phenoxylbenzamine.

We conclude that, after alpha adrenergic blockade, the normal vasoconstrictive response of the cerebral blood flow to hypocapnia is unaffected.

XIV-99

Sympathetic Innervation and Carbon Dioxide Sensitivity—Stone HL, Raichle ME, Hernandez M (Marine Biomedical Institute, Galveston, Texas, and the Washington University Medical School, St. Louis, Missouri)

Cerebral vessels have been demonstrated to be richly endowed with sympathetic fibers that are assumed to innervate the smooth muscle of the vessels. Studies have established that these sympathetic nerves determine the level of cerebral blood flow (CBF) around which autoregulation will occur. The involvement of the sympathetic nervous system in the response of CBF to changes in arterial carbon dioxide has not been studied adequately. It was decided to examine this question in chronically denervated animals. Six Rhesus monkeys were chronically implanted with Doppler flow probes around the left internal carotid artery and both superior cervical ganglia were removed. The animals recovered seven to ten days after surgery and were then anesthetized with phenycyclidine. CBF was manipulated by respiring the animal on room air, 6%, 9%, and 12% carbon dioxide, and also lowering and raising arterial pressure by exsanguination and by aramine infusion. During the room air and acute exposure to carbon dioxide, the Pa_CO₂ was 41 ± 2, 47 ± 4, 57 ± 2, and 66 ± 2 mm Hg, respectively. At a mean arterial pressure of 100 mm Hg, the CBF velocity was 25 ± 2, 27 ± 3, 34 ± 4, and 38 ± 4 cm per second.

Stroke, Vol. 4, May-June 1973
CBF autoregulation (CBFA) was present but shifted to higher flow levels with each successive increase in carbon dioxide. Some CBFA was found at 12% carbon dioxide. Comparison of the CO₂ sensitivity between normal animals and denervated animals revealed a significant decrease (P < 0.05) in sensitivity. Exposure of these animals to 6% CO₂ in a sealed chamber for five days demonstrated that CBFA would adapt and decrease the response to CO₂. The cerebrospinal fluid pH normalized during the period but bicarbonate increased from 22 ± 1 to 32 ± 1 mEq per liter (P < 0.01). Histochemical examination of major cerebral vessels demonstrated at least 90% loss of adrenergic fibers. Evidence indicates that normally CO₂ acts through a change in brain extracellular fluid pH and the change in pH influences the release of norepinephrine from sympathetic nerve terminals. The shift in CBFA during chronic CO₂ exposure may represent a direct vascular smooth muscle effect.

(Supported in part by NASA Contract No. NGR-44-088-002.)

XIV-100 Abnormal Cerebral Blood Flow Regulation in Subjects With Complete Cervical Cord Transection—Eidelman BH, Corbett JL, Frankel H (Department of Neurology, Churchill Hospital, Oxford, and the National Spinal Injuries Center, Stoke Mandeville Hospital, Aylesbury)

Our previous studies carried out on subjects with chronic complete cervical cord transections have suggested absence of cerebral vasconstriction in response to low CO₂. In these studies cerebral blood flow was estimated using Xenon inhalation technique. When Xenon is administered by inhalation, contamination of noncerebral tissues occurs. It has been suggested that the findings reported in these subjects may have been due to vasodilation in extracranial tissues masking a normal constrictor response in the cerebral circulation.

To elucidate this problem, a further study was carried out on subjects with chronic complete cervical cord transections and a control group using cerebral arteriovenous oxygen content differences to provide an index of cerebral blood flow. Observations were carried out at rest and during the course of serial graded decreases in arterial carbon dioxide.

The control group exhibited a progressive fall in cerebral blood flow as arterial carbon dioxide decreased. The tetraplegic group showed a different response. There was little change in arteriovenous oxygen content when PaCO₂ was decreased from a mean resting level of 39 torr to approximately 30 torr. Below this level some increase in A-VO₂ content was noted, but this remained significantly less than that of the control group at the same level of PaCO₂.

Administration of carbon dioxide gas to inspired air resulted in a marked increase in cerebral blood flow in both groups as evidenced by a decrease in the arteriovenous oxygen content. This gives further support for the view that an intact sympathetic nervous supply is necessary for cerebral vasconstriction to occur normally in response to low CO₂.
Methysergide did not change the flow reduction. Cerebral metabolic rate of oxygen was not changed.

Infusion of dopamine in doses varying from 0.05 to 57.4 \( \mu g \) per kilogram per minute was found to cause a reduction of the cerebral blood flow at small doses. This reduction could be abolished by \( \alpha \)-adrenergic receptor blocking. As a result of medium doses of dopamine there was an increase, in some experiments up to 50\% of the control measurement, of the cerebral blood flow. The flow increase could be abolished by dopamine receptor blocking agents as pimozide and haloperidol. \( \beta \)-adrenergic receptor blocking did not change this flow increase induced by dopamine. During infusion of larger doses of dopamine the cerebral blood flow once more decreased. Autoregulation was well functioning both during the flow increase caused by dopamine and when this increase was abolished by pimozide. The cerebral metabolic rate of oxygen was not changed by dopamine infusion.

XIV-103 Evidence for the Adrenergic Control of Cerebrovascular Tone—Rosendorff C, Mitchell G, Scriven DRL (Departments of Physiology and Medicine, University of the Witwatersrand, Johannesburg, South Africa)

Hypothalamic blood flow (HBF) was measured in the conscious rabbit using a \(^{133}\)Xenon clearance technique. Fine cannulae were placed with their tips at the same stereotaxic coordinates on either side of the midline. This allows for the addition of test compounds, such as autonomic drugs, to the \(^{133}\)Xenon-saline injectate on one side, with the other side used as a control. Thus the effect of small doses of these drugs on local flow may be assessed, independent of any systemic effects.

This technique has been used to adduce indirect evidence for the adrenergic control of cerebrovascular tone, at least in this site. Norepinephrine (NE) produced dose-dependent changes in flow: 1 \( \mu g \) per injection caused a mean increase in HBF of 55\%, while doses of 10, 20, 40, and 200 \( \mu g \) per injection reduced HBF by mean values of 26\%, 17\%, 20\% and 29\%, respectively. An intermediate dose, 2 \( \mu g \) per injection, was without any significant effect. The dilator effect of NE 1 \( \mu g \) was blocked by propranolol, and the vasoconstrictor effect of NE 40 \( \mu g \) was blocked by phenoxybenzamine. These findings suggest that there are \( \alpha \)-receptors and \( \beta \)-receptors in the resistance vessels of the hypothalamus, the \( \beta \)-receptors are activated by smaller doses of NE and \( \alpha \)-receptors by larger doses. The net effect of the larger dose is an \( \alpha \)-receptor mediated vasoconstriction.

On the basis of these findings it might be predicted that destruction (e.g., by 6-hydroxydopamine, 6-OH DA) of the sympathetic nerves supplying the resistance vessels of the area would cause increased sensitivity of these vessels to exogenous NE. Intrahypothalamic 6-OH DA (10 \( \mu g \) per injection) produced a denervation hypersensitivity such that NE 2 \( \mu g \) per injection, previously without significant effect, reduced HBF by a mean value of 43\%.

The next series of experiments was designed to determine whether endogenous NE, i.e., NE released by sympathetic nerve terminals, produced similar effects. Tyramine causes the release of endogenous NE; 0.1 ng of tyramine per injection produced a small, nonsignificant increase of HBF, while doses of 0.1 \( \mu g \), 1.0 \( \mu g \) and 10 \( \mu g \) per injection reduced HBF by mean values of 34\%, 36\% and 23\%, respectively. Depletion of NE from sympathetic nerve terminals (proved by histochemical fluorescence studies) by pretreatment of the animals with reserpine (1 mg per kilogram I.M. per day for three days) abolished the vasoconstrictor effect of tyramine 1.0 \( \mu g \) per injection. This suggests that endogenous NE, i.e., NE released from nerve terminals, is vasoactive in "physiological" concentrations.

XIV-104 Sympathetic Nervous Influence on the Blood Circulation and Carbonic Anhydrase Activity in the Choroid Plexus—Edvinsson L, Nielsen KC, Owman CH (Department of Histology and Neurosurgical Clinic A, University of Lund, Lund, Sweden)

The choroid plexus forms a specialized vascular region in which the regulating mechanisms are poorly understood. The existence of nerve fibers and the possibility of a neural influence on CSF production have been much debated. Recent fluorescence histochemical studies (formaldehyde method) have definitely established the presence of adrenergic nerve fibers in all four plexuses from mice, rats, guinea-pigs, rabbits, cats, cows, and monkeys. The studies revealed that several preterminal fibers accompanied the choroidal arteries. Nerve terminals, often in large numbers, ran in between the epithelial cells and the vessel wall in the plexuses, though some areas seemed to be devoid of adrenergic nerves. A surprisingly rich innervation was found around the plexus veins. All nerves disappeared after removal of the superior cervical sympathetic ganglia.

The blood flow and the carbonic anhydrase (CA) activity are two factors known to determine the rate of CSF production from the choroid plexuses. CA was determined in homogenized rabbit plexuses by measuring radioactive CO\(_2\) released from NaH\(^{14}\)CO\(_3\). Test experiments showed that acetazolamide injection (10 mg per kilogram) reduced plexus CA by 60\% within one hour. Since CA is present both in the plexus epithelium and in erythrocytes, nonperfused and saline-perfused plexuses were compared.

Bilateral removal of the superior cervical ganglia almost doubled CA activity in the plexus epithelium (= perfused plexuses) within one week, as compared to sham-operated controls. At the same time, the CA activity accounted for by the plexus blood (= nonperfused minus perfused plexuses) increased twice, indicating a marked increment also in plexus blood volume after sympathetic denervation. The results suggest that the sympathetic nerves in the choroid plexuses exert an inhibition of CSF production through an effect both on the epithelial cells and the blood circulation. The situation thus resembles that of the ciliary body of the eye whose sympathetic nerves are known to inhibit the formation of aqueous humor.
SYMPOSIUM ABSTRACTS

RESERVE
Adrenergic Innervation of Blood Vessels in Certain Regions of the Central Nervous System—Angelakos ET, King MP, Ponessa JT, Irvin JD (Department of Physiology and Biophysics, Hahnemann Medical College, Philadelphia, Pennsylvania 19102)

The fluorescence histochemical technique has been used to study the adrenergic nerve terminals (ANTs) associated with blood vessels in the CNS in a number of laboratory species including the rat, rabbit, cat, squirrel monkey, Rhesus monkey and baboon. Distinct ANTs associated with blood vessels were found in many regions of the medulla, pons, hypothalamus, thalamus and basal ganglia. The vessels of the spinal cord were similarly innervated. Small vessels in the cortex and cerebellum did not have ANTs. However, adrenergic fibers were found in all large blood vessels of the CNS. The vessels in the pia membranes had an extensive supply of ANTs. Microspectrophotometric studies indicated that the ANTs associated with blood vessels had a more intense fluorescence than ANTs found within the CNS parenchyma (e.g., in hypothalamic nuclei) suggesting that they contain a higher intraneuronal concentration of catecholamines. Denervation and stimulation studies in the cat indicated that most of these ANTs originate from adrenergic neurons in the superior cervical ganglion. Significant decreases in hypothalamic and thalamic blood flow were observed on direct or reflex stimulation of these fibers. Reflex vasoconstriction was found in hemorrhagic shock. These results suggest that blood flow through certain key regions of the CNS is under adrenergic control.

SUMMARY: P. Scheinberg

Session XV: Neurogenic Control II

FRIDAY (2:00 TO 3:45 P.M.)

CHAIRMAN: W. FEINDEL
CO-CHAIRMAN: F. GOTOH

XV-105
Effect of Sympathetic Nerve Stimulation on Cerebral and Cephalic Blood Flow—Traystman RJ (present address: Department of Environmental Medicine, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland 21205), Rapela CE (Department of Physiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103)

Sympathetic nerves related anatomically to cerebral blood vessels have been demonstrated; however, the role these nerves may play in the control of cerebral vasomotor tone is controversial. Most investigators have observed that the cervical sympathetic system has no, or only slight, effect on the cerebral vasculature. More recently it has been shown that stimulation of dog stellate ganglion, or nerves arising therefrom to the superior cervical sympathetic ganglion, produces marked constriction of the cerebral vasculature. The effect of stimulating the stellate ganglion has been studied in dog cerebral and cephalic blood flow via a cervical and thoracic approach under sodium pentobarbital, chloralose anesthesia, and two different stimulation voltages (3V and 5V). Monophasic pulses, 10 ms duration, 3 or 5V, at 14 cycles per second were applied for a one-minute period. Cerebral venous blood flow was measured at the confluence of the sagittal, straight, and lateral sinuses with the lateral sinuses occluded. Stellate ganglion stimulation resulted in no change in cerebral blood flow with either of the anatomical approaches, the anesthetics or the voltages used. The common carotid ipsilateral to the nerve stimulated was then isolated and carotid blood flow measured with a non-cannulating electromagnetic flow probe. Stimulation of the stellate ganglion induced a marked decrease in common carotid blood flow (40% of control) and dilation of the ipsilateral pupil, but showed no change in cerebral blood flow. Similar effects were observed with each of the anatomic approaches, the anesthetics and the voltages used. Stellate ganglion stimulation also resulted in a decrease in the blood flow measured at the confluence of the sinuses (85% to 90% of control) but only when the lateral sinuses were kept patent. A decrease in common carotid blood flow also was observed. Stenosis of the extracranial venous circulation by clamping both external jugular veins increased the blood flow measured at the confluence of the sinuses. Under these conditions, the decrease in blood flow measured at the confluence of the sinuses with stellate ganglion stimulation was significantly increased (60% to 70% of control).

Stimulation of the stellate ganglion either by a cervical or thoracic approach, or under sodium pentobarbital or chloralose anesthesia, or with two different stimulation voltages, has no effect on the cerebral vasculature. "Measured" cerebral blood flow was decreased significantly by sympathetic stimulation only when communications between intracranial and extracranial venous vasculatures were present.

(Supported by NIH Grants HL 00487, 05392 and N. C. Heart.)
Regional Brain Blood Flow During Sympathetic Stimulation—Meyer MW, Klassen AC (Departments of Physiology and Neurology, University of Minnesota, Minneapolis, Minnesota 55455)

Controversy exists as to the extent that sympathetic stimulation modifies blood flow to the brain. Blood flow to the right (r) and left (L) side of the brain and selected bilateral regions were studied during unilateral sympathetic stimulation (s) and nonstimulation or control (c) conditions. The particle distribution method was used to determine these flows in five anesthetized dogs. Sympathetic fibers distal to the left caudal cervical ganglion were stimulated (20 to 30 Hz, 5 to 10 V, 3 to 5 msec in duration) with a bipolar electrode. The left ventricle was catheterized to inject a known quantity of radioactive microspheres (~25 μm in diameter) 30 seconds after initiating stimulation. After recovery a second quantity of differently labeled microspheres was injected. Reference flows for each injection were obtained by arterial sampling, beginning prior to injection and continuing for about 20 seconds thereafter. The ratio of radioactivity in each sample to the corresponding reference flow provided values for the integrated activity time curves (A/g). Following sacrifice, activities per unit weight (A/g) of the two labels in right and left sides of the brain and regional samples of brain stem, pons, cerebellar and cerebral cortex, cerebral white, thalamus and caudate were determined. Flow/g (F) was calculated as (A/g)/A_t. For the two sides of the brain, (F_r)r = 0.66, (F_r)l = 0.70, (F_L)r = 0.77 and (F_L)l = 0.75. The ratio of left and right side (F/L) values averaged 0.95 (0.85 to 1.05) and (F_l/F_r) was 1.07 (0.87 to 1.33). For the regional samples, these ratios ranged from 0.96 to 1.06 and 0.87 to 1.12, respectively. Ratios were not significantly different from 1.0 and (F_l/F_r) values were not significantly different from (F_l/F_r) values. P_a in mm Hg, ranged from 24 to 64 mm Hg. By the particle distribution method, unilateral sympathetic stimulation does not appear to reduce brain blood flow to the stimulated side. (Supported by NIH Grant No. NB 03364.)

Autonomic Control of Cerebral Blood Flow and Autoregulation—Hernandez-Perez MJ, Erickson HH (Environmental Sciences Division, USAF School of Aerospace Medicine, Brooks AFB, Texas 78235)

Although the presence of sympathetic and parasympathetic nerves in intracranial arteries is well established, the function these nerves have in the control of cerebral circulation is not fully understood. In this study, 26 macaque monkeys were chronically instrumented with a Doppler ultrasonic flow transducer around the left internal carotid artery. Two to three weeks after surgery, arterial blood pressure and carotid flow were measured while the monkeys were lightly sedated with phencyclidine hydrochloride. Cerebral blood flow (CBF) was monitored during exsanguination and infusion of metaraminol through a catheter in the femoral vein while the animal breathed ambient air or a mixture of 9% CO2 in air. Phenoxybenzamine (1 mg per kilogram) was administered intravenously or by cisternal puncture to 14 monkeys in order to define the effects of alpha-adrenergic activity on the cerebral arteries. In another group of 12 monkeys, atropine (200 μg per kilogram) was administered by intravenous and cisternal routes in order to produce parasympathetic blockade. Administration of phenoxybenzamine resulted in a 34% decrease in mean arterial blood pressure and an 18% increase in mean carotid flow. Cerebral blood flow autoregulation (CBFA), however, was essentially maintained over a pressure range from 70 to 160 mm Hg during exsanguination and infusion of metaraminol. Atropine elicited a significant tachycardia but no effect on arterial pressure, CBF, or CBFA, while the monkeys breathed either ambient air or 9% CO2. These results suggest that CBF and CBFA are only subtly modulated by the sympathetic innervation of the cerebral vasculature, since this process persists even when alpha-adrenergic activity is blocked. The parasympathetic nerve fibers do not appear to influence CBF or CBFA at all.

Cholinergic and Adrenergic Innervation of Cerebral Vessels—Licata RH, Olson D, Mack E (Reno, Nevada)

The existence of a regulatory mechanism making for control of cerebral circulation continues to be the subject of intensive study. The authors have demonstrated by prior studies the conclusive evidence of the presence of catecholamine fibers within the adventitia of the cerebral arteries and veins. The present work demonstrates the presence of cholinergic fibers in all segments of the cerebral arterial circulation. A dual mechanism therefore exists, responsible for neural regulation of cerebral flow.

The presentation consists of a film and slides demonstrating both cholinergic and adrenergic innervation of cerebral vessels in animal and human material.

Adrenergic innervation is demonstrated by means of autofluorescence. The technique utilized to demonstrate the cholinergic system employs a modification of the Koelle-Friendewald method staining acetylcholinesterase. Pseudo-cholinesterase has been inactivated by the addition of OMPA.

Structures believed to be parasympathetic ganglia are demonstrated consistently in pia and dura in and around Stroke, Vol. 4, May-June 1973
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anterior midline structures. These ganglia appear to be of two types: a smaller, probably visceral, afferent; and a larger, probably visceral, efferent. Speculation as to origin and function is elaborated upon.

XY-110 Cholinergic Receptors at Pial Arteries. A Microapplication Study—Kuschinsky W, Wahl M (Department of Physiology, University of Munich, West Germany)

Morphological studies have suggested the existence of cholinergic nerve fibers at pial arteries, which might indicate cholinergic-mediated vasodilatation of cerebral vessels. In contrast, isolated cerebral arteries respond with vasoconstriction to acetylcholine. In order to study under in vivo conditions the existence of cholinergic receptors in pial arteries, carbacholcholine, a parasympathomimetic substance, was applied locally to the perivascular site of pial arteries by micropuncture technique and its effect upon pial arterial diameter measured. These experiments were performed on anesthetized cats with controlled ventilation and acid-base status. Following trepanation, pial arterial diameter was measured by means of the TV image splitting method of Baez. Carbacholcholine was dissolved in mock spinal fluid which itself had no vascular effect. Concentration response curves for carbacholcholine were obtained from single pial arteries. Carbacholcholine in concentrations between $10^{-10}$ and $10^{-4}$ M per liter had no vascular effect. A concentration-dependent dilation was observed at concentrations between $10^{-5}$ to $10^{-4}$ M per liter. The maximal increase in vascular diameter at $10^{-4}$ was 20%. These results suggest the existence of cholinergic dilating receptors. In order to evaluate a possible contribution of cholinergic vascular receptors to the vascular tone under these experimental conditions, the effect of perivascularly applied atropine on vascular diameter was studied. At concentrations between $10^{-6}$ and $10^{-4}$ M per liter atropine exerted a dilating effect (18%) which is considered to be nonspecific. A specific action of atropine would (in any case) lead to vasoconstriction because of the dilating action of carbacholcholine.

XY-111 Cholinergic Innervation of the Pial Arterial System—Nielsen KC, Edvinsson L, Owman CH (Neurosurgical Clinic A and Department of Histology, University of Lund, Lund, Sweden)

Cholinesterase histochemistry in combination with proper inhibitors is at present the only technique for selective demonstration of cholinergic nerves at the light microscopic level. Such nerves were demonstrated in fresh whole-mounts of pial arteries from mice, rats, rabbits, hamsters, guinea-pigs, and cats.

All pial arteries received a varying degree of cholinergic nerve supply. The arteries deriving from the carotid system had the largest number of nerves, a particularly dense plexus being present around the anterior and middle cerebral arteries. Arteries from the vertebral system contained fewer nerves, for example, as seen in the posterior cerebral and the cerebellar arteries. The quite large number of fibers around the basilar artery often ran in thick bundles. As a general feature, the nerve supply very much resembled that previously described by us for the adrenergic system. In fact, experiments were performed in which arterial preparations were first treated in formaldehyde gas (for visualization of fluorescent adrenergic nerves), photographed and then incubated with acetylthiocholine and Mipafox (to demonstrate cholinergic nerves) followed by re-photography: it turned out that the cholinergic nerves ran together with the adrenergic fibers in the same strands of the autonomic plexus. Electron microscopy confirmed this arrangement and, further, showed that the membranes of the two types of nerve terminals often came as close as 250 Å, offering a possibility for axo-axonal interrelations between the cholinergic and adrenergic fibers. The adrenergic ones, but not the cholinergic, disappeared after bilateral superior cervical gangliectomy. Axo-axonal contacts also occurred in the neuro-effector area, where the naked nerve endings were located about 1,000 Å from the membrane of the arterial smooth muscle. This distance is similar to that found in the neuromuscular areas of peripheral vessels known to be controlled by autonomic nerves. Thus, the structural requirements for a true cholinergic (as well as adrenergic) innervation of the pial arterial system are fully satisfied. Accordingly, acetylcholine was found to exert profound vasomotor effects, abolished by atropine, on isolated pial arteries (but not extracranial arteries) from cat and man.

RESERVE

The Innervation of Cerebral Arteries in the Cat—Cervos-Navarro J (Klinikum Steglitz, Freier Universität, Hindenburgdamm 30, Berlin 45, Germany)

It is common opinion that most of the arterioles of the brain have no nerve fibers, in contrast to all other organs.

In order to check this assumption about 100 cerebral arterioles with a diameter between 5 and 20 μ of the frontal, parietal, and occipital gray and white matter of cats were examined by electron microscopy. About 40% of the vessels had nonmyelinated nerve fibers the rate of arterioles with myelinated nerve fibers was 80%. The nerve fibers were confined to the outer surface of the media. Three types of arrangements were observed: (1) Bundles of 10 to 15 axons. In these cases only a short or no mesaxon could be seen. The Schwann cell processes usually surrounded the axons incompletely so that parts of the axon circumferences were naked. The axon bundles and associated Schwann cell sheath were surrounded by a basement membrane. (2) Groups of two to four axons. On cross section they could be identified only by their characteristic cytoplasmic structures. Schwann cell processes and a mesaxon were missed. Only a few of these axon groups were surrounded by a basement membrane. (3) Isolated nerve fibers. They, too, were not associated with Schwann cells.

The largest axons of groups 1 and 2 contained mitochondria, neurotubules, and vesicles. Occasionally the vesicles contained a granulated mass. The isolated fibers of group 3 could frequently be identified by their

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granular vesicles. The nerve fibers were always separated from the surface of the muscle cells by a gap of about 20 mm. There was no evidence for postsynaptic structures of muscle membranes attached to any of the different types of nerve fibers.

The data obtained so far do not allow any conclusions concerning the function of cerebral arterial innervation. But they obviously may serve as a basis for the discussion of neurogenic control of cerebral blood flow.

SUMMARY: W. Feindel

Session XVI: Neurogenic Control III
FRIDAY (4:00 TO 5:45 P.M.)
CHAIRMAN: A. HARPER
CO-CHAIRMAN: E. NELSON

XVI-112
Effect of Alpha and Beta Adrenergic Blocking Agents on Regional Cerebral Blood Flow and CO₂ Responsiveness in Patients With Cerebrovascular Disease—Mathew NT, Meyer JS, Hartmann A (Department of Neurology, Baylor College of Medicine, and the Baylor-Methodist Center for Cerebrovascular Research, Houston, Texas 77025)

Although morphological evidence suggests the presence of adrenergic nerve terminals and receptors in the cerebral vasculature, the extent of their influence on cerebral blood flow (CBF) regulation in health or disease is not clearly defined.

Thirty-nine patients with cerebrovascular disease had determinations of regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV) and the degree of responsiveness of rCBF to induced changes in Paco₂ before and after the intracarotid injections of alpha adrenergic blocking agent, phenoxybenzamine (PBZ), or beta adrenergic blocking agent, propranolol (PPL).

Regional cerebral blood flow and rCBV were measured by the gamma camera after serial injections of 133Xe and 99m Tc.

The effect of PBZ on rCBF and rCBV was influenced by changes in arterial blood pressure and capacity of the brain to autoregulate. It produced slight increases in rCBF and rCBV in ten patients whose blood pressure remained unaltered as a result of PBZ administration, whereas 13 patients in whom the drug caused hypotension showed a significant reduction in rCBF and rCBV (P < 0.001). Six of the above 13 patients, tested in the same laboratory using the hydrogen technique for measuring CBF, were found to have dysautoregulation.

PBZ relieved cerebral vasospasm of major arteries in patients with acute subarachnoid hemorrhage, and increased rCBV, but did not improve rCBF nor alter the responsiveness to hypercapnia or hypocapnia.

PPL produced a significant fall in mean hemispheric rCBF (11.8%, P < 0.01 and rCBV with maximum reduction in patients with acute hypertensive intracerebral hemorrhage (35.2%, P = < 0.005). Responsiveness to hypercapnia was significantly reduced after PPL, with no significant changes in the responsiveness to hypocapnia.

The effect of adrenergic blockade on rCBF in patients with cerebrovascular disease is modified by factors such as dysautoregulation and alteration in the blood-brain barrier which permit direct metabolic effects on the blocking agents on ischemic brain. The present study suggests minimal if any influence of the beta system on the vasodilator response to hypercapnia; the alpha system was not found to influence the vasomotor response to changes in Paco₂, although this has been reported to occur in normal persons.

(This work was supported by Grant NS 09287 from the National Institute of Neurological Diseases and Stroke, and in part by Grant RR 00350 from the General Clinical Research Centers Branch, Division of Research Resources, National Institutes of Health, Bethesda, Maryland 20014.)

XVI-113
The Upper Limit of Autoregulation and the Sympathetic System—Skinhøj E (Bispebjerg Hospital, Copenhagen, Denmark)

In previous publications we have shown that in man blocking of the sympathetic nervous system with phentolamine does not affect CBF, its autoregulation against decreasing blood pressure, or the CO₂ reactivity. The probable possibility remains that the sympathetic system might play a protective role against a dangerous high perfusion pressure in case of severe hypertension.

To test this possibility we examined a group of hypertensive and normotensive patients to see whether or not the upper limit was changed by blockade of the sympathetic system.

During controlled hypertension by means of angiotensin and by measuring CBF, partly directly with the intracarotid 133Xenon method, partly indirectly by determination of (A-V) oxygen difference over the brain, we reached the point of "break through," i.e., the point where a further increased blood pressure results in an increased CBF and a decreased (A-V) oxygen difference.

After returning to the habitual blood pressure of the patient the procedure was repeated, but this time after blocking of the sympathetic system either by blockade of the stellatum ganglion or by use of 20 mg phentolamine intravenously. We found no evidence of a decreased "break through" point after the sympathetic blockade.

XVI-114
Autoregulation of Cerebral Circulation in Orthostatic Hypotension—Shinohara Y, Gotoh F (Department of Neurology, Keio University School of Medicine, Tokyo, Japan)

In our previous report in Roma, it was shown that there was a loss of autoregulation of cerebral vessels in patients with Shy-Drager syndrome in which the autonomic nervous system is known to be involved. Therefore, it was presumed that the autonomic nervous system plays an important role in the mechanism of autoregulation.

In order to confirm the relationship between cerebrovascular autoregulation and autonomic nervous function, we have further investigated 37 patients with or without orthostatic hypotension which was considered to be one of the signs indicating dysfunction of autonomic nervous system. Autoregulation was estimated from the effect of head-up tilting on CBF. CBF was
Evidence for Autoregulation in the Human Retinal Circulation—Ross Russell RW (Institute of Neurology, National Hospital, Queen Square, London, and St. Thomas' Hospital, London, England)  

The relative importance of neurogenic, myogenic and humoral factors in regulating the tonus of cerebral arteries is still disputed. It is known that retinal arteries react to changes in oxygen tension and to infusions of noradrenaline or angiotensin, but the latter observation cannot distinguish between constriction as a myogenic response to a change in blood pressure or as a humoral response to a circulating vasoactive agent. This difficulty can be resolved by using a mechanical stimulus of another kind, by external pressure on the globe. This raises the intraocular tension and reduces the pressure gradient across the walls of the retinal arteries without altering systemic blood pressure. A change of caliber which occurs under these conditions must be produced by myogenic factors.  

The caliber of retinal arteries (diameter 50 to 150 μ) was measured by a fluoroangiographical method in normal patients and in patients with oculosympathetic paralysis before and after raising intraocular tension by pressing lightly on the globe with an ophthalmodynamometer. Systemic blood pressure was unchanged.  

A significant increase in diameter of about 15% was found in arteries but not in veins when intraocular tension was raised, in both normal patients and those with sympathetic paralysis. The change occurred within two minutes of altering the intraocular tension and the magnitude of the change was similar in the two groups.  

This reaction is likely to be a local myogenic reflex (Bayliss effect) independent of innervation and concerned with autoregulation of retinal blood flow.
Resistance changes in the smaller arteries of the brain were observed only when the alterations of the perfusion pressure were too big and the major arteries were unable to eliminate the disturbances.

The "autoregulatory" responses of the internal carotid arteries were eliminated when their muscular layer was maintained normal in relevance to the responses to vasoactive substances, but was completely deprived of the nervous control (i.e., when after death of the animal the arteries were continuously perfused with blood from a donor-dog or with the oxygenated Ringer-Krebs bicarbonate solution). Thus, direct evidence was obtained that the vascular responses controlling the constant blood supply to the brain in the face of changes of the perfusion pressure were brought about by a nervous and not by a purely muscular mechanism, as was usually assumed.

Correlation Between Oxygen Cycles in Contralateral Regions of the Brain—Burgess DW (Royal Naval Physiological Laboratory, Fort Road, Alverstoke, Hants, England)

In the measurement of cerebral tissue oxygen variations are observed that appear to be cyclic. At the last Symposium it was suggested by Severinghaus (1971) that these cycles were due to open-shut cycling of the capillary bed under control of brain CO₂. If this form of cycle control were correct, the result should be a random cycling of the tissue oxygen in the various regions of the brain. No correlation in the cycles should exist in equal regions of the contralateral hemispheres.

Data observed by this author conflict with this idea, as experiments on non-anesthetized animals have shown that the cycles are in phase in equal regions of the two hemispheres. Rats were implanted with two gold polarographical electrodes under sodium pentobarbital anesthetic, care being taken to ensure that the two probes were in equal regions of the contralateral hemispheres, i.e., left and right medial geniculate. One week was then allowed for the animals to recover from surgery. After recovery the rats were connected to a feedback polarographical recorder and the brain oxygen level monitored. Feedback was used in the polarographical recorder to minimize the effect of brain potentials changing the reference level, and producing a false oxygen change.

The data from the oxygen probes were analyzed on a PDP 11 computer using FFT and convolution techniques to determine the frequency and phase of the oxygen cycles. Final analysis was made on these data using cross-correlation to determine the relationship between the records from equal points in the two hemispheres under a variety of experimental conditions.

Analysis of this type indicates a main frequency band in the range of 5 to 8 cycles per minute that has marked correlation in both frequency and phase in the two hemispheres. This indicates that the oxygen cycles are not random and independent but that they are coupled from some central source.

XVI-118

Correlation Between Oxygen Cycles in Contralateral Regions of the Brain—Burgess DW (Royal Naval Physiological Laboratory, Fort Road, Alverstoke, Hants, England)
SYMPOSIUM ABSTRACTS

mitochondrial incubation system was applied to animals subjected to moderate to severe ischemia produced by hypotension and hypoxia. With moderate ischemia (five minutes), mitochondria doubled their formation of ATP without further augmentation after adding GABA while with severe ischemia (eight minutes) little ATP was formed. Our results suggest that in mildly ischemic brain, the endogenous elevation of GABA plays a role in enhancing mitochondrial supply of high energy phosphate.

(Supported by NIH Grants NS-07769 and NS-09128.)

XVII-120

Comparative Effects of Various Metabolic Inhibitors on Cerebral Hemodynamics, Electrical Activity and Cation Transport—Baldy-Moulinier M (Département de Pathologie Expérimentale, Institut de Biologie, Montpellier, France)

Regulation of CBF and of membrane ionic transport in the brain seems to be linked by a coupling mechanism. If the disturbances of the cerebral ionic distribution by cerebral ischemia are well known and attributed to an energy deficiency, the influence of the "sodium pump" activity on CBF remains unresolved. The active movement of cations, especially of potassium ions, is presumed to act as a pacemaker on the regulation of CBF, of sodium pump activity and cerebral electrical activity.

It has been shown previously that blocking the ion pump of the cell membrane by intraventricular administration of ouabain, an inhibitor of the membrane Na-K ATPase, caused a release of intracellular potassium into the extracellular space which was associated with cerebral hyperemia and secondary ischemia.

In the present study cerebral hemodynamic changes were analyzed in correlation with EEG and cerebral ionic distribution, after intracarotid or intracisternal administration of different metabolic inhibitors such as cyanide, 2-4 dinitrophenol, cycloheximide and purine, presumably acting on a particular site of the energetic metabolism.

The experiences were performed on cats which were anesthetized, curarized, and artificially ventilated for an arterial P O2 of 29 mm Hg. CBF was determined by 133Xenon clearance. EKG, femoral arterial pressure, and electrical activity of the cortex and hippocampus were continuously recorded. Body temperature, arterial blood pH, P O2, P CaO2, osmolarity and ionic concentrations (Na +, K +, Cl -) of cisternal CSF were controlled. Animals were transiently submitted to arterial pressure and P O2 changes to test the cerebral vasomotor reactivity. Electron microscopic analysis of the brain was made on some animals.

Injections of metabolic inhibitors into the internal carotid produced variable changes of CBF partly influenced by modifications of heart rate and systemic blood pressure.

The intracisternal injections of the same inhibitors in doses four times lower than those used for intracarotid administration produced the following constant changes.

Intracellular potassium release as evidenced by increase of CSF potassium, transient rise of arterial pressure, long-lasting cerebral hyperemia, loss of autoregulation, vasomotor unresponsiveness to PaCO2 changes, and depression of electrical activity. The importance and the duration of these modifications were different according to the type of the metabolic inhibitors.

Cyanide, which inhibits the production of high energy phosphates and chiefly affects the neuronal elements, induced an important intracerebral potassium release into CSF (K + concentrations rose from 2.8 ± 0.3 mEq per liter to 7 ± 0.5 mEq per liter), a rise of systemic blood pressure for five minutes, an increase of CBF to average 250% of control maintained for at least 60 minutes, a rapid loss of autoregulation, a delayed cerebral vasoparalysis to PaCO2 changes, and a prolonged electrical silence. Progressive return to normal of these parameters was observed in the following order: ionic CSF concentration, CBF, CO2 reactivity of the cerebral vessels, electrical activity and CBF autoregulation. Repeated injections of cyanide did not cause a cerebral circulatory arrest except when the heart rate was depressed.

2-4 DNP, which inhibits the active energy-consuming mechanism of transportation, induced an increase of CSF potassium from 2.8 ± 0.3 mEq per liter to 5.2 ± 0.2 mEq per liter, a rise of CBF to 200% of control for 30 minutes followed by a progressive decrease. Electrical silence only occurred when CBF fell about 60%. Secondary cerebral circulatory arrest without heart and arterial blood pressure changes was possible.

Cycloheximide and purine which inhibit protein synthesis caused a weak increase of CSF potassium to 3.6 ± 0.3 mEq per liter, no rise of arterial pressure, and an increase of CBF only to 30% of control, followed by a progressive and slight decrease of CBF and a depression of EEG. Electrical silence and cerebral circulatory arrest never occurred. Cerebral vascular reactivity was not altered.

These results confirm the relationship between extracellular potassium concentration, cerebral hyperemia and modifications of cerebral electrical activity. Hemodynamic, metabolic, and morphological conditions of secondary cerebral circulatory arrest will be discussed.

XVII-121

Potassium Effects on Energy Metabolism and Epileptiform Activity in the Cat Hippocampus—O'Connor M, Lewis D, Herman C (Branch of EEG and Clinical Neurophysiology, NINDS, Bethesda, Maryland; and Division of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania)

Levels of intramitochondrial NADH*, using a surface fluorometer, and electrocorticography were monitored in the intact cat hippocampus. The effects of topically applied K + and ouabain were recorded. It was found that when the K + concentration in the topically applied artificial CSF was increased from 4 mEq per liter to 20 mEq per liter the NADH* level declined within one to two minutes manifesting increased energy
metabolism. Further increases of K\(^+\) concentrations to 30 mEq per liter produced no further decline in NADH\(^+\) but often resulted in seizures. At higher K\(^+\) concentrations (54 mEq per liter) the NADH\(^+\) usually rose. These effects of K\(^+\) on NADH\(^+\) levels could be blocked by 5 \times 10^{-5} \text{ mM} \text{ ouabain}, a blocker of the sodium pump.

The above data are interpreted as reflecting increases in energy metabolism due to stimulation of the sodium pump by elevated levels of extracellular K\(^+\). The fact that ouabain blocks this increase strongly supports this hypothesis. The lack of further increase in energy metabolism when the K\(^+\) concentration is between 20 and 30 mEq per liter as well as the subsequent decrease in energy metabolism with higher K\(^+\) concentrations can be explained by noting that in vitro measurements with the sodium pump, have shown that the activity of this enzyme reaches maximum and then declines in this range of K\(^+\) concentrations.

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**XVII-122**

**Prognostic Value of Carbohydrate Metabolites in CSF—**

"The Luxury Glucose Supply" of the Brain—Molnár L

(Departments of Neurology and Psychiatry, University of Debrecen Medical School, Debrecen, Hungary)

1. Immediately after clinical death, i.e., just following the stop of respiration and circulation, the glucose, pyruvate and lactate content and the value of lactate-pyruvate ratio are significantly higher in the CSF, while the pH values are significantly lower than those of the controls. Some hours later the glucose content and the pH of the CSF successively decrease, and the pyruvate and lactate content, just like the value of the lactate-pyruvate ratio, increase.

2. In fatal cases, regardless of the disease, before death a gradual increase of glucose content in CSF is regularly observable, usually together with increase of the lactate content and the value of lactate-pyruvate ratio.

3. Throughout the recovery of patients having cerebral infarct, the glucose content and the value of lactate-pyruvate ratio in the CSF gradually decrease. In contrast to this in cases when the patients die, the mentioned values increase.

4. In epileptics, the CSF contains significantly more glucose right after a seizure than in interictal periods. There is no correlation between the glucose content and the type of the seizure. The increase of glucose content is followed by that of the lactate content only in one part of the cases.

These observations clearly prove that change of the glucose content in the CSF is a valuable prognostic sign, which is at least as much or more sensitive and consistent than the change of lactate content or the value of lactate-pyruvate ratio.

Increase of glucose content in the CSF may, of course, be caused by the altered functions of barriers. However, the changes in the blood-CSF/glucose, pyruvate, lactate, pH/ratios more possibly suggest that the nervous tissue, damaged by any reason, is not able to use the glucose physiologically. In such cases one part of the glucose, carried by the blood flow, is utilized by glycolysis, while the other part is unused in those circumstances, and enters the CSF without transformation. This process can be designated as "luxury glucose supply."

**XVII-123**

**In Vivo Measurement of Cerebral Glucose Metabolism Employing \(^1\text{C}\) Labeled Glucose—Raichle ME, Phelps ME, Larson KB, Grubb RL Jr, Welch MJ, Ter-Pogossian MM (Washington University School of Medicine, St. Louis, Missouri)

At the present time there is no method available for the in vivo measurement of regional cerebral glucose metabolism in man. We present here the results of experiments in monkeys which establish the foundation for such a tool employing the gamma-ray emitting isotope, carbon-11, which decays by positron emission. The 511 kev annihilation radiation readily penetrates soft tissue and bone, thus allowing easy external detection, localization and measurement in vivo. Glucose is labeled by photosynthesis and purified in a period of one hour yielding a sterile, pyrogen-free solution.

The isotope is injected intravenously as a bolus. A single suitably collimated sodium-iodide detector is placed under the head for recording brain activity and a second probe is placed over an external extension of an indwelling peripheral arterial catheter and blood withdrawn to describe the arterial blood curve. The count rate information from each of the two probes is integrated over one-second time intervals for a collection period of two minutes and processed in a classic LINC computer. This relatively short collection period provides ample data for analysis while minimizing the problem of isotope egress from the brain.

To correct the reading obtained from the head for activity contained in blood, the nondiffusible tracer carbon monoxide containing 15O is used. The correction is accomplished by multiplying the carbon-11 activity in blood with the ratio of brain to blood C15O activity and subtracting the result from the head reading. Since the glucose activity in scalp, muscle and bone is mainly in blood, this effectively corrects for all extracerebral contamination.

The resultant data, a brain tissue curve and an arterial curve, are analyzed by procedures set forth in a mathematical model developed to yield quantitative cerebral glucose utilization rates. This model takes into account the isotope labeling effect of the cerebral free glucose pool through incorporation of a mechanism of facilitated diffusion for transport of glucose across the blood-brain barrier.

To test this model, the cerebral metabolic rate for glucose (CMR\(_{Glu}\)) was determined in 15 pentothal-anesthetized monkeys concurrently by the present carbon-11 method and by the Fick principle employing H\(^2\)O for the measurement of CBF. Cerebral venous blood was obtained from the superior sagittal sinus via a chronic indwelling appliance. CMR\(_{Glu}\) determined by the Fick principle varied from 2.04 to 6.03 mg/100 gm per minute. A highly significant correlation was found between the two methods (CMR\(_{Glu}\) [carbon-11] = [1.02 ± 0.05] CMR\(_{Glu}\) [Fick] + 0.01 ± 0.58, r = 0.89, P < 0.001).
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This method would thus appear to offer an acceptable means of measuring regional CMR$_{glue}$ in man when employed with a properly designed multiprobe system. The risk is minimal because arterial catheterization is limited to peripheral sites. Modification of the model currently in progress shows promise of reducing this risk and increasing patient acceptability by substituting peripheral venous catheterization.

XVII-124
A Method for Serial Study of Regional Cerebral Blood Flow and Metabolism—Simone FA (Assistant Professor of Neurosurgery, University of Pennsylvania School of Medicine, and Chief, Neurosurgery, Pennsylvania Hospital, 800 Spruce Street, Philadelphia, Pennsylvania 19107)

Current studies which can measure metabolism in a specific region of brain are limited either because freezing techniques make the preparation unavailable for serial studies, or because the techniques themselves allow only the study of one specific aspect of metabolism (fluorometry, radioactive oxygen consumption, etc.). Valid metabolic data have been obtained by sampling of jugular or cerebral sinus venous blood, but this reflects metabolism of the entire brain and, perhaps, extracerebral structures. Experimental cerebral angiography was performed on a series of monkeys, and subsequently barium arterial casts of these brains were made. Anatomical dissection revealed that a large vein in the posterior parietal region drains cortex supplied only by branches of the middle cerebral artery. This was confirmed by retrograde injection of micropulverized barium into the cannulated vein. In the monkey, this vein traverses a distance of 9 mm across the parietal parasagittal cortex before emptying into the superior sagittal sinus. It receives three tributaries which supply the cortex of the parietal lobe above the Sylvian fissure. All of the barium-injected cortical arteries which bore direct relationship to this vein could be traced to the superior branch of the middle cerebral artery.

With microsurgical techniques, this vein can be cannulated bilaterally, and the venous outflow fed into a calibrated Y-connector, which in turn empties by catheter into the jugular vein. Regional cerebral blood flow measurements by the Krypton 85 washout technique in the cortex drained by this vein are not changed after the cannulation. Multiple injections of 0.2 mCi Krypton 85 were made at various points in the cerebral cortex at a depth of 1 mm. Radioactivity of the venous outflow from this system was counted one minute after each injection, and the territory of drainage of the vein was accurately "mapped." Branches of this vein, which run in parallel sulci, drain the blood only from their adjacent gyri. Radioactivity in this venous blood was detected only with injections into the cortex supplied by the middle cerebral artery. Simultaneous serial cerebral blood flow recordings in this cortex were correlated with the rate of venous outflow over a wide range of flow alteration produced by hypotension, CO$_2$ inhalation, and hypertension. Cerebral blood flow changed from 31 ml/100 gm per minute to 142 ml/100 gm per minute. Venous outflow ranged from 0.3 ml per minute to 1.6 ml per minute. The relationship between regional cerebral blood flow and venous outflow was linear throughout these variations.

These data suggest that metabolites which can find their way into venous blood can be measured serially in a known area of cortex correlated with blood flow. This conveniently located "vascular-metabolic unit" is easily accessible for recording. direct pH measurement, fluorometry, polarographic oximetry, focal cortical sampling, etc.

XVII-125
A Study of P$_{O_{2}}$ in Cerebrospinal Fluid During Clinical Anesthesia—Kubota T (Duke University Medical Center, Box 3094, Durham, North Carolina 27710), Matsuda I, Tachbana N, Kawaguchi T, Yamamura H

The direct measurement of brain tissue oxygen tension, which is one of the most important parameters in brain physiology and pathophysiology, is not easily attainable in clinical practice because of great technical difficulties. The measurement of CSF P$_{O_{2}}$ has been proposed by several investigators as a guide determining oxygen availability to the brain. The validity of CSF P$_{O_{2}}$, however, is yet to be established.

This study was designed to assess the value of lumbar CSF P$_{O_{2}}$ as an index of cerebral oxygenation during clinical anesthesia. The first experiment was undertaken to determine the relationship between changes in CSF P$_{O_{2}}$ and changes in P$_{aCO_{2}}$ and CSF lactate, excess lactate and L/P ratio during N$_{2}O$-O$_{2}$-curare anesthesia. The possibility that cerebral hypoxia may be induced by severe hypocapnic hyperventilation during N$_{2}O$-O$_{2}$-curare anesthesia also was examined. In order to confirm the possibility of cerebral hypoxia, the relationship between somatosensory-evoked response on EEG (EVR) and CSF P$_{O_{2}}$ and CSF lactate, excess lactate and L/P ratio was investigated in a second experiment. In addition, a comparison of cerebral oxygenation and metabolism between halothane-N$_{2}O$-O$_{2}$ anesthesia and N$_{2}O$-O$_{2}$-curare anesthesia was undertaken.

The P$_{O_{2}}$, acid-base status and lactate, pyruvate concentrations of CSF, of arterial blood and, in six cases, the evoked response of EEG were measured in 36 patients. Constant controlled pulmonary hyperventilation was utilized in all cases, regulation of P$_{aCO_{2}$ being achieved by adjusting fresh gas flow in a circuit from which the soda lime was removed. Before induction of anesthesia, a specially designed epidural catheter was carefully inserted into the subarachnoid space at the level of the third lumbar interspace. CSF and arterial blood were sampled before induction of anesthesia and at one, two and three hours after the start of hyperventilation. Analyses of samples were done with a strictly anaerobic technique. P$_{O_{2}}$, pH and P$_{CO_{2}}$ were determined with a Radiometer-Astrup microelectrode. Lactate and pyruvate were determined by standard enzymatic methods. In order to get EVR, a digital computer of the on-line type was used. Stimulation of the median nerve was made percutaneously by a single pulse delivered from an electronic stimulator.

The mean CSF P$_{O_{2}}$ breathing room air was 44.8 torr at a mean P$_{aCO_{2}$ of 35.5 torr. The regression line

**Stroke, Vol. 4, May-June 1973**
When severe hypocapnic hyperventilation was applied, a formula was expressed as: $y = 0.8 \times + 16.0$ (torr), $Se = 5.92$ obtained from $N_2O-O_2$-curare anesthesia and room air.

During hyperventilation, it decreased gradually and finally approached that in the $N_2O$ group. During the first hour of hyperventilation, no significant change in lactate and $L/P$ ratio was found. In the second experiment, when EVR was plotted on semilogarithmic paper against CSF $P_{O_2}$, lactate, excess lactate and $L/P$ ratio respectively, significant correlation between EVR and every parameter except for $L/P$ ratio were observed; that is, when EVR diminished, a fall of CSF $P_{O_2}$ and a rise of CSF lactate and excess lactate were found. In the third experiment, blood-CSF $P_{O_2}$ difference showed a decrease during halothane anesthesia in contrast to an increase during $N_2O-O_2$-curare anesthesia after the initiation of hyperventilation. Simultaneously CSF $P_{O_2}$ showed a significant difference between both groups. Although CSF $P_{O_2}$ in the halothane group was maintained at a higher level than that in the $N_2O$ group during hyperventilation, it decreased gradually and finally approached that in the $N_2O$ group. During the first hour of hyperventilation, no significant change in lactate level was observed in the halothane group in contrast to a significant increase in the $N_2O$ group. When excess lactate and $L/P$ ratio at the third hour were compared with the control, a significant increase was observed in the $N_2O$ group while no change was detected in the halothane group.

On the basis of these findings lumbar CSF $P_{O_2}$ appears to be an acceptable indicator in determining oxygen availability to the brain. The effects of anesthesia and hypocapnia on cerebral tissue oxygenation and metabolism will be discussed on the basis of the changes found in CSF $P_{O_2}$ and CSF lactate, excess lactate, $L/P$ ratio and EVR values.

### XVII-126
**The Question of Uncoupling of Cerebral Oxidative Phosphorylation in Acute Cerebral Infarction**—Meyer JS, Shimazu K, Okamoto S, Koto A, Itoh Y, Sari A, Giri NY, Ericsson AD (Department of Neurology, Baylor College of Medicine, and the Baylor-Methodist Center for Cerebrovascular Research, Houston, Texas 77025)

Free fatty acids (FFA) have been reported to accumulate in ischemic brain and uncouple oxidative phosphorylation. This may explain why oxygen consumption continues in an acutely infarcted hemisphere despite hemiplegia and unilateral EEG slowing.

This study was designed to measure concentrations, in arterial and cerebral venous blood and CSF, of relevant cerebral substrates which might indicate any uncoupling before and after infusion of 10% glycerol or phenoxybenzamine (PBZ) in patients with acute cerebral infarction.

**Results**

- **Energy change potential**: $ECP = \frac{\text{ATP} + \text{ADP} + \text{AMP}}{\text{ATP} + \text{ADP} + \text{AMP}}$

- Hemispheric cerebral blood flow (HBF) was measured using the hydrogen bolus method. Cerebral oxygen consumption ($CMRO_2$), glucose consumption ($CMRGI$) and CO₂ production ($CMRCO_2$) were monitored on a polygraph. Cerebral arteriovenous differences and CSF concentrations of other metabolites were sampled before and after glycerol treatment.

- For the first 14 days after infarction, concentrations of FFA and inorganic phosphate (Pi) were significantly higher in cerebral venous than arterial blood, indicating that infarcted brain leaked both substances; after 14 to 21 days cerebral A-V differences approached zero. Catecholamine concentrations in CSF correlated inversely with the duration of infarction and directly with $CMRO_2$, while serotonin concentrations in CSF were inversely related to both duration and HBF. Infarcted brain also leaked cyclic AMP into cerebral venous blood.

- Intravenous infusion of 500 ml of 10% glycerol increased HBF significantly and reversed the release of cyclic AMP. Both glycerol and PBZ reduced $CMRO_2$ and $CMRGI$, and reversed the release of FFA and Pi. Reduction in cerebral oxidative metabolism by both treatments was associated with improved neurological function as judged by EEG, respiration and neurological status.

- In conclusion, FFA and catecholamines accumulate in infarcted brain, probably resulting in uncoupling of cerebral oxidative phosphorylation. Infusion of glycerol or phenoxybenzamine during acute infarction apparently recouples oxidative phosphorylation and/or improves production of high energy phosphate bonds with improved neurological function.

- (This work was supported by Grant NS 09287 from the National Institute of Neurological Diseases and Stroke, and in part by Grant RR 00350 from the General Clinical Research Centers Branch, National Institutes of Health, Bethesda, Maryland 20014.)

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**SYMPOSIUM ABSTRACTS**

**XVII-127**

**The Effect of Controlled Hyperventilation on the Energy and Acid-Base States of the Rat Brain**—Nilsson L, Busto R (Cerebral Vascular Research Center, the Department of Neurology, University of Miami School of Medicine, Miami, Florida)

Of both theoretical and practical interest has been the problem of whether hyperventilation produces a hypoxic effect on the brain. Although hyperbaric oxygen reverses the EEG slowing of hyperventilation, and brain and CSF lactate increases with HV while elevating NADH/NAD+ and La/Py ratios, these evidences of tissue hypoxia have not been found to be accompanied by significant decreases in labile phosphate compounds of the tissue, leaving in some doubt the confirmation of hypoxia. To study the effects of HV on tissue energy metabolism and acid-base balance, six groups of Wistar rats were subjected to study at time intervals of 10, 45, and 180 minutes after HV to values of $P_{CO_2}$ of 20 to 25 torr in three groups and 10 to 15 torr in three more groups.

**Energy change potential**

$ECP = \frac{\text{ATP} + \text{ADP} + \text{AMP}}{\text{ATP} + \text{ADP} + \text{AMP}}$

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and cytoplasmic NADH/NAD+ (= La/Py × K+/H+) were calculated, and tissue HCO3~ and pH were derived with qualifying assumptions.

HV induction produced a lactic acidosis and increased La/Py ratio in arterial blood and CSF, but the changes diminished as HV was prolonged despite an unchanging PCO2. Blood glucose increased progressively to 180 minutes. Neither moderate nor extreme hypocapnia produced any detectable decreases in tissue ATP but did cause marked increase of La/Py and a fall in glucose. Intracellular values were similar to changes in blood and CSF except for the glucose change. The La/Py change was most marked early but tended toward normalization with continued HV. HV produced marked CSF alkalisos, which tended to normalize despite maintenance of elevated arterial blood pH. Derived tissue pH was slightly increased at all times during moderate HV, but by contrast, the extreme hypocapnic groups showed significantly lower intracellular pH at 10 and 45 minutes. At three hours the pH had returned to control values.

Only at ten minutes of extreme HV did ECP show a significant decrease. The NADH/NAD+ ratio showed increases at first in all groups but slowly returned to control values at three hours HV.

Moderate HV did not change brain tissue energy state. Extreme HV transiently depleted ECP, principally noted in a transient elevation of ADP. Elevated tissue pH activates phosphofructokinase which probably allowed the increased tissue La and Py through accelerated glycolysis, and this together with decreased blood flow may be the cause for decreased tissue glucose initially in both hypocapnic groups.

Extreme hypocapnia appears to induce hypoxic lactic acid production and it is possible that this acid production counteracts further vasoconstriction and increased hypoxia. The explanation for normalization of tissue La and Py with continued HV is not able to be offered.

RESERVE

Cerebral Autoregulation and Metabolism With Deep Hypothermia—White RJ, Wolin LR, Taslitz N, Austin JC, Austin PE Jr (the Department of Neurosurgery, Case Western Reserve University School of Medicine; at Cleveland Metropolitan General Hospital, the Brain Research Laboratories, Cleveland, Ohio 44109).

While previous studies conducted in the isolated primate brain model have suggested loss of autoregulation in the cerebral circulation at profound hypothermic temperatures, little is known referable to the circulatory performance of the brain in situ at these deep thermal ranges. These experiments, utilizing a simple physiological method of differentially cooling the primate brain, were employed to examine these phenomena.

Thirteen Nembutalized Rhesus monkeys were tracheally intubated and instrumented for: arterial pressure, EEG, EKG, intracerebral (thalamic) and rectal temperatures, and lateral sinus sampling (brain venous blood). Profound differential brain hypothermia was accomplished using autocerebral perfusion cooling (femoral-unicarotid arterial shunt with the interposition of only a high efficiency-low pressure drop heat exchanger). All other cervical arteries including both external carotids were temporarily occluded during cooling. CBF was measured with an electromagnetic flowmeter over the single carotid perfusing brain. To minimize the effects of cooling on blood viscosity, low molecular dextran was employed to reduce the hematocrit to 30. Each animal was heparinized and the cephalon packed in ice. Body core temperature was maintained above 35°C with surface heating units.

With the initiation of "self cooling" of brain the CBF was initially reduced 1.3 cc/min/°C from a normothermic average of 40.5 cc per minute. However, below 25°C the cooling curve tended to flatten out with CBF averaging only 0.5 cc/min/°C drop. At 20°C significant hypotension (average 80/50) and bradycardia (85 per minute) were invariably encountered with CBF of less than 11 cc per minute, resulting in extreme difficulty in further lowering brain temperature. The addition of small increments of catecholamine (0.032 mg Levophed) again produced sustained reductions in intracerebral temperature (1 cc/1°C/min) to 5°C with transient increases in arterial pressure (180/120 to 90/60) and CBF (30 to 15 cc per minute).

Arteriovenous O2 measurements during cerebral cooling demonstrated a progressive fall. Normothermic values of 6.4 vol % were reduced to 2.5 vol % at 20°C. Between 8° and 5°C intracerebral A-V O2 differences tended to equalize with catecholamine support of systemic circulation.

These experiments demonstrate for the first time the ease of manipulating CBF via systemic pressure at profound hypothermic temperatures, suggesting suspension of cerebral circulatory autoregulation below 20°C as well as the expected severe reductions in cerebral metabolic activity at these temperatures.

(Research supported by NIH Grant No. NB-03859.)

SUMMARY: E. Betz

Session XVIII: Summary and Discussion
Cerebral Circulation and Metabolism Sixth International CBF Symposium

Stroke. 1973;4:321-379
doi: 10.1161/01.STR.4.3.321
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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