The Conference opened on Wednesday, January 9, 1974, with a presentation by Dr. Richard L. de C. H. Saunders (Research Professor, Instituto da Rocha Cabral, C. Bento da Rocha Cabral No. 14, Lisbon, Portugal), entitled “Anatomy of the Cerebral Microcirculation.” Dr. Saunders used microangiography to study and make pictures of 30 to 70 μ diameter blood vessels. He showed numerous pictures of the circulation to occipital cortex, temporal lobe, and some deeper structures.

Following a presentation, “Autonomic Control of Cerebral Blood Flow,” by Mr. A. Murray Harper (Reader in Surgical Physiology, Wellcome Surgical Research Institute, University of Glasgow, Garscube Estate, Bearsden Road, Glasgow, Scotland), discussion of the problems of control of cerebral blood flow was continued by Dr. Peritz Scheinberg (Professor of Neurology, University of Miami School of Medicine, Miami, Florida). No conclusion was reached concerning the relative importance of sympathetic nerve stimuli in the control of cerebral circulation in the human or whether these stimuli are even of significant clinical interest. In animal experiments it is apparent that there are elements of cerebral blood control which are affected by metabolic factors while others are influenced by the autonomic nervous system.

The program for Thursday, January 10, 1974, opened with “Experimental Cerebral Vasospasm” by Dr. S. J. Peerless (Assistant Professor of Neurosurgery, University of British Columbia, Vancouver, British Columbia, Canada). He commented that in subarachnoid hemorrhage in humans there are two ways to clinically define the term vasospasm. The first is essentially “any patient who does badly following the rupture of an intracranial aneurysm,” and the second is the appearance of narrowed arteries at angiography. Prolonged spasm is of importance, and in man it appears that delayed spasm also is important. Noradrenalin may be found at considerable distances from actual subarachnoid hemorrhage, and Dr. Peerless pointed out that the uptake of this substance is different, conceptually, than the accumulation of it. He went on to add that the relationship, in man, between what is called cerebral vasospasm and catecholamines is uncertain and that actual failure of inactivation of noradrenalin may be important in the pathogenesis of the narrowing. There may be a triggering of a cascade of contractile substances, all of which interrelate, including angiotensin and calcium. It may be necessary to stop the very first step in this chain or cascade in order to actually prevent cerebral vasospasm.

Dr. John F. Alksne (Professor of Neurology,
University of California at San Diego, San Diego, California) discussed the presentation and summarized his view of the clinical pathogenetic situation by mentioning that: (1) subarachnoid hemorrhage causes loss of intraneural catecholamines, (2) following subarachnoid hemorrhage there is accumulation of catecholamines in smooth muscle cells, (3) vasospasm caused by blood can be eliminated by the alpha blocker phenoxybenzamine, and (4) there is often an elevated blood level of catecholamines in subarachnoid hemorrhage, which correlates with the blood pressure and electrocardiographical findings.

He added that in his own observations in the laboratory, watching the patterns of reaction in the basilar artery following the injection of noradrenalin, spasm comes, then disappears, then returns and often persists for several days, without a further injection of the noradrenalin. Electron microscopic studies reveal that the artery had damaged muscle cells, as long as several days after the pathophysiological process. Dr. Alksne added that the word "vasospasm" may be a misnomer — that is altogether likely that the term should be "vasonecrosis." It was particularly interesting to note that the actual experimental animal (the monkey) appeared to show no clinical change during the time there was "vasospasm!" In addition, he pointed out that with light microscopy no abnormalities of any kind were observed in the artery study.

During the open discussion, Dr. Terland Nelson (Professor of Neurology, University of Maryland School of Medicine, Baltimore, Maryland) mentioned that he had noted the same electromicroscopic changes presented by Dr. Alksne in normal arteries and wondered whether the changes presented were of any significance at all. The matter was left unresolved.

Dr. Mannie M. Schechter (Professor of Radiology, Albert Einstein College of Medicine, Bronx, New York) presented material concerning the views of a neuroradiologist about clinical cerebral vasospasm. Dr. Schechter said that he preferred to define "cerebral vasospasm" simply as an altered state of reactivity of the cerebral vessels and customarily subdivided such altered reactivity into local and diffuse types. Dr. Schechter displayed many reproductions of arteriograms which demonstrated this altered reactivity.

Dr. Clark H. Millikan (Professor of Neurology, Mayo Medical School, Rochester, Minnesota) discussed the subject of the clinical state of patients with cerebral vasospasm. Dr. Millikan emphasized the need to have some objectivity in defining the term "cerebral vasospasm." He reminded the Conference members that already that morning Dr. Peerless had commented that there are two ways to clinically define the term: (1) "any patient who does badly following the rupture of an intracranial aneurysm," and (2) "the appearance of narrowed arteries at angiography." It is apparent that if one uses the first of these definitions, the term "vasospasm" becomes meaningless and will be used incorrectly to describe situations which include cerebral infarction, cerebral hemorrhage, diffuse brain ischemia, and the syndrome of inappropriate antidiuretic hormone.

Dr. Millikan reported preliminary observations concerning Mayo Clinic experience, beginning January 1, 1968. Patients included must satisfy the following criteria: (1) a clinical history compatible with a diagnosis of acute primary subarachnoid hemorrhage with the onset within the preceding ten days, (2) bloody cerebrospinal fluid (nontraumatic tap), (3) cerebral angiogram interpreted by a neuroradiologist showing one or more cerebral aneurysms (saccular, berry). For purposes of study, spasm is defined as the objective interpretation of this phenomenon in the neuroradiologist's formal written report. Of the first 100 patients observed, over 40% had vasospasm (as reported by the neuroradiologist). Of those patients having intracranial surgery, the mortality was higher in the group without vasospasm than in the group with vasospasm. Of those surgical patients who died, 78% had no spasm while 22% had spasm. Of those patients not having surgical treatment (26 individuals), the mortality was 33% for those who had spasm and 50% for those who had no spasm. Of those patients who had surgery the complication rate was slightly higher for the group without spasm than for the individuals with spasm. There was absolutely no evidence that any particular clinical state, including various alterations of consciousness or any pattern of focal neurological abnormalities, was significantly associated with radiological evidence of cerebral vasospasm.

The next presentation was by Dr. Thoralf M. Sundt, Jr. (Associate Professor of Neurosurgery, Mayo Medical School, Rochester, Minnesota), who talked about the "Management of Cerebral Vasospasm." Dr. Sundt described a treatment with a combination drip of isoproterenol and lidocaine hydrochloride. This method of management is based on the hypothesis that the cerebral sympathetic nerve supply in the conducting vessels of the subarachnoid space serves as a modulating and buffer function to protect the cerebral vessels from vasoconstrictive agents in the blood and cerebrospinal fluid. Following subarachnoid hemorrhage there is loss of fluorescence of the granulated vesicles indicating their inactivation. In contrast with cholinergic endings in which the function of freed acetylcholine is terminated by an enzyme, limited duration of action of adrenergic endings is thought to be related to the prompt reuptake of norepinephrine by the granulated vesicles. Loss of this buffered function sensitizes the alpha receptor sites. Isoproterenol, a beta adrenergic drug, is used to provide a relative vasoconstrictor which may function in this system primarily by tying up or jamming a receptor site. The lidocaine hydrochloride is administered to
preclude cardiac irregularities that can occur with the use of isoproterenol.

Dr. Charles E. Drake (Professor of Neurosurgery, University of Western Ontario, London, Ontario, Canada) opened the discussion. He commented about their observations concerning 280 postoperative angiograms but did not give any information which would correlate the appearance of the angiogram with the type of focal neurological abnormality the patient might or might not have. There was no real change in the incidence of spasm after an early or delayed operation. It was noted that patients operated upon later after bleeding did very much better than patients operated upon early, even though the former had just as much spasm as the latter. Dr. Drake went on to mention that the treatment of postoperative spasm has been quite unrewarding as a whole, in spite of a variety of techniques and agents. Dr. Drake went on to add that their efforts at producing effective vasodilatation had not been rewarding. He concluded by reporting about the experience in 19 cases from which it seemed evident that dibenzyline had very little effect in established spasm.

Many questions were raised — time ran short and the discussion had to be terminated.

"Experimental Production of Miliary Aneurysms With Hypertension" was presented by Dr. Charles A. Santos-Buch (Department of Pathology, Cornell University Medical College, New York, New York). Dr. Santos-Buch described the experimental production of miliary aneurysms of small-sized arteries of the brain and the iris of hypertensive albino rabbits. He believes that these experimentally produced miliary aneurysms have morphological characteristics similar to those associated with the intracerebral miliary aneurysms originally described by Charcot and Bouchard in man. The histological changes were cellular disarrangement and/or fibrinoid or lipohyaline alterations in the media, principally in the area of the internal elastic lamina — sometimes associated with a mild inflammatory alteration. One hundred to two hundred micron-sized vessels were involved. Dr. Santos-Buch showed scanning electron microscopic pictures of ulcerations in the endothelium, which he believes constitute the first stage of miliary aneurysm production. It was noted that the occurrence of brain hemorrhages progressively increased with the worsening of the degree of iridoarteriopathy.

Dr. C. Miller Fisher (Professor of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts) opened the discussion by pointing out that Charcot and Bouchard had never actually published any photographs of their aneurysms but only pictured drawings. Dr. Fisher wondered whether such things actually exist as currently interpreted. He went on to present slides of a variety of small aneurysms, most of them being due to what he calls lipohyalinosis.

Dr. Nelson asked whether the scanning electron microscope abnormalities might simply be artifacts of the technique, as he has seen similar phenomena in normal vessels. There was no way of settling this matter.

Dr. Philip A. Wolf (Assistant Professor of Neurology, Boston University School of Medicine, Boston, Massachusetts) presented material from the Framingham study as he discussed "Hypertension as a Risk Factor for Stroke." There have been 196 strokes in the Framingham population under observation during 18 years. Sixty percent of these have been cerebral thromboses, 17% subarachnoid hemorrhage or intracerebral hemorrhage, 18% cerebral emboli, and the category 'other' represents 5%. Dr. Wolf noted that the incidence of stroke rises in proportion to the elevation of blood pressure.

Dr. John H. Laragh (Professor of Clinical Medicine, Columbia-Presbyterian Medical Center, New York, New York) presented "The Occurrence of Stroke in Hypertensive Patients With Elevated Renin Activity." He has found that elevation of renin and aldosterone produces a heart attack and stroke-prone profile. He went on to point out that patients with low renin have a low incidence of stroke, those with normal renin have a high incidence of stroke, and those with high renin have a high incidence of stroke. He believes that chronic vasospasm is associated with the level of renin and pointed to hypertensive encephalopathy as an example of this.

Discussion of the role of blood pressure in stroke occurrence was opened by Dr. William J. Mroczek (Georgetown University, Medical Division, District of Columbia General Hospital, Washington, D.C.), who did not agree with Dr. Laragh's hypothesis that the level of plasma renin activity may be related to the occurrence of vascular disease in hypertensive patients. Dr. Mroczek studied a group of black hypertensive patients, plotting the 24-hour sodium excretion versus the plasma renin activity. Forty-three of 452 patients had a documented history of myocardial infarction or stroke. Forty-seven percent of these were in the low renin group, 42% in the normal renin group, and 11% in the high renin group; therefore, the distribution of patients with stroke and myocardial infarction was identical to that of the general hypertensive population. Finally, Dr. Mroczek pointed out that after reviewing the world literature concerning the subject, he must conclude that the relationship between renin levels and vascular disease cannot be substantiated.

During the open discussion Dr. Ralph W. Richter (Associate Professor of Neurology, Columbia University, College of Physicians and Surgeons, New York, New York) emphasized that strokes are particularly severe in young black hypertensives and said that the importance of treating the elevated blood pressure, particularly in this group, could not possibly be ex-
There were 143 patients whose diastolic pressures
aggrated. Dr. Laragh, in response to Dr. Mroczek's
criticism, simply said that the two of them did not
agree.

The effect of treatment of hypertension on stroke
occurrence was discussed by Dr. Edward D. Freis
(Senior Medical Investigator, Veterans Administra-
tion Hospital, Washington, D.C.), who summarized
other workers' observations by noting that there
appears to be a reduced frequency of stroke when high
blood pressure is controlled. Dr. Freis described the
Veterans Administration Cooperative Study, which
was a perspective, randomized, double-blind trial
carried out in 523 male patients with initial diastolic
blood pressures in the range of 90 to 130 mm Hg. The
trial was terminated after an average follow-up of only
18 months in this subgroup of patients because of a
highly significant difference in morbid events in the
group as compared to the treated patients.

Stroke occurred in five of the control patients and in
one of the treated patients. The remaining 380 patients
whose initial diastolic blood pressures were in the
range of 90 through 114 mm Hg were observed for an
average follow-up period of 3.3 years, while some were
observed for as long as five years. The incidence of
strokes in these patients were 20 in the control group
and five in the treated group. The effectiveness of
treatment was greatest in patients under the age of 60
years although effectiveness was demonstrated at all
ages.

Following Dr. Freis, Dr. Raymond B. Bauer
(Professor of Neurology, Wayne State University
School of Medicine, Detroit, Michigan) presented
material concerning "The Effect of Treatment of
Hypertension on Recurrence of Stroke." The material
he presented was from the Hypertension-Stroke
Cooperative Study Group, who compared
deserpine-thiazide and placebo in 452 patients who
had a stroke in the previous year. The mean blood
pressure was 167/100 and the mean age was 59 years.

Over a mean follow-up period of three years the stroke
recurrence rate was 17% for the treated group and 19%
for the untreated group — not a significant
statistical difference.

The formal discussion was opened by Mr. A.
Barham Carter (Consulting Neurologist, Ashford
Hospital, Middlesex, England), who found the result
reported by Dr. Bauer to be disappointing. Mr. Carter
suggested three points which should be considered
before the treatment of moderate hypertension in
stroke survivors is abandoned. These were: (1) it is
easier to control hypertension effectively by individual
doses of medication rather than by a fixed dose, (2) do
not treat patients unless their systolic pressure is
above 160 mm Hg or the diastolic pressure is above 95
mm Hg, and (3) when actually treating, it is necessary
to get both the systolic and diastolic pressures to nor-

Mr. Carter related that in his own experi-
ence in a randomized trial concerning 99 patients
with stroke with hypertension, the four-year mortality
was reduced from 46% to 26% and the recurrence rate
from 44% to 20% when one compared untreated with
treated patients.

Open discussion did not bring out any new con-
cepts concerning the importance of detecting, properly
diagnosing, and adequately treating systemic high
blood pressure.

Dr. Donald Nibbelink (Assistant Professor of
Neurology, University of Iowa, Iowa City, Iowa)
reported for the Cooperative Aneurysm Study on
"Antihypertensive and Antifibrinolytic Therapy
Following Subarachnoid Hemorrhage From Rupt-
ured Intracranial Aneurysm." This study sum-
marizes the results of randomized use of antihyperten-
sive drugs alone, antifibrinolytic therapy alone, and
their combination in 242 patients. Chlorothiazides,
methyldopa, reserpine, and hydralazine, alone or in
combination, were used to produce drug-induced
hypotension. This treatment category was defined as a
20% reduction in systolic blood pressure under 140
mm Hg, a 25% reduction in pressure between 140 and
180 mm Hg, and a 30% reduction over 180 mm Hg
with respect to the average of four prerandomized
systolic values. The antifibrinolytic therapy consisted
of epsilon-aminocaproic acid, 24 to 36 gm per day,
oral or intravenous route of administration, or tranex-
amic acid (a potent antifibrinolytic agent used ex-
clusively by some overseas participants). The other
category was drug-induced hypotension and an-
tifibrinolytic treatment. Each treatment program was
initiated within seven days and continued through 14
days following the last bleed. During the two-week in-
terval, 28.9% died among those who received drug-
induced hypotension, 5.8% died among the an-
tifibrinolytic group, and 23.8% died in the combined
therapy group. In addition, angiographical visualiza-
tion of arterial narrowing was measured at each in-
vestigating center. Detailed analysis of patients who
had their angiographical survey on each day following
the last lesion revealed that from days four through
seven, a greater percentage were likely to show some
degree of vasospasm with comparison to those whose
angiographical survey was done prior to day four.
Analysis of death and presence of vasospasm revealed
no statistically significant correlation, although mor-
tality was 10% more in those manifesting some degree
of vasospasm. Neither was proved rebleeding
significantly more in the group with vasospasm com-
pared to those without vasospasm.

Discussion of Dr. Nibbelink's presentation was
opened by Dr. John T. Girvin (Assistant Professor of
Neurosurgery, University of Western Ontario, Lon-
don, Ontario, Canada). He reported that he and his
colleagues have studied the effect of antifibrinolytic
therapy (epsilon-aminocaproic acid) in the treatment
of acute subarachnoid hemorrhage. One group of patients received the medication — another group did not. Dr. Girvin found no differences at all in the mortality rate from rebleeding in the two groups!

Dr. John F. Mullan (Professor of Neurological Surgery, University of Chicago Hospitals, Chicago, Illinois) commented about relating the dose of the medication to the accelerated clot lysis time and the relationships of results to antihypertensive treatment. The issue about the impact of epsilon-aminocaproic acid remained unsettled.

Discussion was continued by Dr. Anthony Fletcher (Associate Professor of Medicine, Washington University School of Medicine, St. Louis, Missouri). He pointed out that Dr. Nibbelink and his colleagues used a dose of epsilon-aminocaproic acid which is a high one. Dr. Fletcher cautions about the potential clinical toxicity but added that in his own experience there has not been a great tendency for the development of thromboembolic vascular complications in those treated.

Dr. Fred Plum (Professor of Neurology, Cornell University Medical Center, New York, New York) gently raised the question about the results of the Cooperative Study by suggesting that if the cooperators had really gotten a mortality of only 5% in patients with subarachnoid hemorrhage it would seem that this is certainly the best treatment — that surgery should be abandoned and that we really had the answer to the whole subject! Dr. Plum was probably getting at the core of the issue. There is nationally almost complete skepticism that the mortality of subarachnoid hemorrhage can be reduced to 5% by the use of epsilon-aminocaproic acid.

The discussion of "Extracranial-Intracranial Arterial Anastomoses" was to have been presented in detail by Dr. M. G. Yasargil (Department of Neurosurgery, Kantonsspital Zurich, Zurich, Switzerland) — Dr. Yasargil was not available and in his classical note of epidemiological pessimism: after that time the difference between treated and untreated patients lessens over a period of five years of observation. The blood pressure levels were the same in treated and untreated patients. It was particularly interesting that among patients treated with anticoagulants, 5% had an intracranial hemorrhage compared with 4% among untreated patients. Dr. Whisnant pointed out that there was no significant difference in age-corrected survival between the treated and untreated groups when one, three and five-year points on the group were compared. At the end of one year the net probabilities of having a stroke for the treated group were 12% and 23% for the untreated group. The largest proportion of strokes occurred among all patients, especially untreated ones, in the first few months after the first TIA. If treatment with anticoagulant is considered, it should be started immediately after a TIA, for maximal possible effect.

Discussion was opened by Dr. John F. Kurtzke (Professor of Neurology, Georgetown University School of Medicine, Falls Church, Virginia). He mentioned that the 2:1 difference in favor of anticoagulants seems to support the long-term use of such treatment. He noted that, on the other hand, the late difference between treated and untreated groups was judged to be statistically insignificant. He then emphasized that Dr. Whisnant’s study still does not support the conclusion that only short-term anticoagulation is warranted. Dr. Kurtzke’s reason for this statement was that short-term anticoagulation was not evaluated! Dr. Kurtzke concluded with a classical note of epidemiological pessimism: after years of looking at the data of experienced observers, he is unable to form any opinion about whether one should anticoagulate patients with transient ischemic attacks.

Thursday evening, January 10th, was devoted to presentations concerning "Computerized Transaxial Tomography (EMI Scan) in the Diagnosis of Cerebral Vascular Disease" by Dr. H. L. Baker, Jr. (Associate Professor of Radiology, Mayo Clinic, Mayo Medical School, Rochester, Minnesota) and Dr. Paul F. J.
New (Associate Professor of Radiology, Massachusetts General Hospital, Boston, Massachusetts). Dr. Baker summarized observations made by him and his colleagues concerning computer-assisted tomography of the head, which has been used for the first time in the United States, in a series of 500 patients at Mayo Clinic. It appears that this technique represents a major advance in neuroradiological diagnosis and in the care of patients with neurological disorders. Computer-assisted tomography of the head is non-invasive — without morbidity. Analysis of the results in these first 500 patients revealed a rate of diagnostic error slightly in excess of 3.5%. This rate compared favorably with such rates associated with other standard neuroradiological procedures in use at Mayo Clinic. It was interesting to note that of the first 100 patients, 71 required one or more neuroradiological procedures for ultimate diagnosis, while of the fifth group of 100 patients having computer-assisted tomography of the head, only 34 required such study.

Dr. New, in experience with more than 300 examinations, reported that the accuracy of the examination is exceptional. It was noted that the presence of gas or any radiopaque material in the ventricles and/or subarachnoid spaces can seriously interfere with the accuracy of readings in the vicinity of this material and that the EMI scan should, if possible, precede the use of these contrast materials.

The first speaker Friday morning was Dr. Plum who presented "The Energy Metabolism of the Brain and Cerebral Vascular Disease." Dr. Plum, in opening his remarks, asserted that any discussion of the energy metabolism of the brain focuses on ATP as a center point. This is because: (1) ATP is a high energy compound, (2) ATP occupies an intermediate position on the thermodynamic scale of phosphate compounds, and (3) there are no enzymes in cells that can directly transfer phosphate groups from high energy donors, generated during the oxidation of food stuffs, to low energy acceptors. However, it continues to be of interest that the brain's overall oxygen use rate seems to be as great during sleep or daydreaming as in wakefulness or vigorous mental activity. Anesthesia, hypothermia, and hypoxia are a variety of pathological states affecting the brain do lead to a reduction of cerebral metabolism, but the items of particular interest to this discussion are those cerebral or systemic conditions that threaten the brain either because they increase its energy requirement or because they cut down on the brain's delivery of energy substrates. Generalized seizures substantially increase the energy use rate of the brain, presumably because of an increase in the requirement to pump sodium and potassium in order to repolarize the massively and repeatedly depolarized neuronal membranes.

Hypoglycemia reduces substrate supplied to the brain and prevents both glycolysis and cellular respiration by cutting the processes off at their source. Hypoxia, as usually encountered clinically, produces a somewhat less immediate threat than anemia because of the shape of the oxygen hemoglobin dissociation curve. Ischemia produces a situation in which the effects of blocking the supply of energy substrate can be difficult to separate from the failure to drain potentially toxic waste products. Oligemia, an incomplete reduction in blood flow, produces more interpretable changes and has the additional advantage of being a process that repeatedly occurs in patients with cerebral vascular disease. During hypoxemia-oligemia, mild to moderate reductions in the adenine nucleotide reserves occur in both hemispheres. Some experiments have shown that the proportion of damaged cells, though histologically evident, may not be large enough to affect the chemical results or the neurons can recover in normal energy content after a transient anoxic-ischemic injury. Total deprivation of substrate cannot be compensated for, however, which is why complete ischemia poses so severe a threat.

Dr. Thomas E. Duffy (Assistant Professor of Neurology, Cornell University Medical College, New York, New York) then discussed the "Effects of Anoxia and Ischemia on Perinatal Brain Metabolism." Dr. Duffy reported the results of studies in rats which demonstrated the fetal rat's tolerance to anoxia. Compared with postnatal animals, Dr. Duffy could not explain the long survival of fetuses in nitrogen on the basis of differences in resting levels of cerebral energy reserves or metabolic rates of the forebrain. However, since maturing and developing animals exhibited selective vulnerability, regional variations in cerebral energy requirements may play a role in anoxic survival. Fetal resistance to anoxia seems to be a prerequisite for the continued well-being of the infant during birth. Animals delivered vaginally manifest profound alterations in cerebral glycolysis and energy metabolism, indicative of an asphyxial insult to brain during the birth process. Some of the changes which were noted immediately after delivery were comparable to changes seen only after five minutes of complete ischemia. The complications of birth, which might superimpose an additional hypoxic or ischemic insult on the fetal organism, would potentiate the threat of perinatal brain injury.

Dr. Kyuya Kogure (Assistant Professor of Neurology, University of Miami School of Medicine, Miami, Florida) began a presentation concerning "Alterations of Energy State With Cerebral Ischemia." Cerebral infarction of various sizes was produced by the injection of carbon microspheres, 35 μ in diameter, into the internal carotid artery of the rat. The early presence of metabolic changes was noted in both hemispheres. The mechanism by which this was brought about was not clear. Dr. Kogure thought that he had excluded the possibility of cross embolization in the experiments. Decreased norepinephrine content was noted in both
hemispheres. This might be due to the release of catecholamine in both hemispheres with vasocostriction thus producing the bilateral ischemic metabolic changes noted. There was marked inhibition of cyclic AMP in both hemispheres, noted first in the infarcted hemisphere, but observed soon afterward in the noninfarcted hemisphere.

This was followed by a presentation by Dr. John D. Michenfelder (Associate Professor of Anesthesiology, Mayo Medical School, Rochester, Minnesota) concerning "The Influence of Anesthesia in Ischemia on the Cerebral Energy State." Dr. Michenfelder summarized a number of studies done in his laboratory in recent years — studies concerning anesthetics and the effect of anesthetics on cerebral metabolism, including the metabolism of cerebral ischemia. In summarizing the results and implications of these experiences, Dr. Michenfelder concluded that barbiturates (specifically, thiopental) can be protective in the ischemic functioning brain but one should not expect it to be protective in the ischemic nonfunctioning brain. Halothane, on the other hand, appears to have a functional effect on cerebral oxygen consumption and in high concentrations has a direct metabolic toxic effect.

Dr. Martin Reivich (Professor of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania) next presented some observations concerning "Alterations of NADH in Cerebral Ischemia." The studies performed had been undertaken in order to directly measure the changes in pyridine nucleotide redox state when cerebral perfusion pressure was changed either by lowering mean arterial pressure or by increasing intracranial pressure. When cerebral perfusion pressure was reduced to approximately 60 mm Hg, significant changes in the redox state of the pyridine nucleotides was first noted and these progressed until complete ischemia was produced when there was approximately an 18% change. This was maintained for one to six minutes of complete ischemia. The change increased to a mean value of about 28% with a maximum value of 50% to 60%. As cerebral perfusion was increased again by lowering intracranial pressure a small change in perfusion pressure (10 mm Hg) was associated with recovery of the fluorescence changes. It required a cerebral perfusion pressure of between 70 and 80 mm Hg for a full recovery to occur. Fluorescence changes occurred earlier when cerebral perfusion pressure was altered by lowering the mean arterial pressure than when the effect was produced by increasing the intracranial pressure. Dr. Reivich believed that further studies will be necessary to determine what, if any, role mild hypoxia plays in the metabolic changes observed with moderate reductions in cerebral perfusion pressure well within the autoregulatory range.

The discussion of these papers was opened by Dr. Richard S. Kramer (Division of Neurosurgery, Duke University Medical Center, Durham, North Carolina). He disagreed with Dr. Michenfelder on several points. He noted that Dr. Michenfelder proposes that the sole effect of barbiturates is to inhibit energy-requiring cellular reactions, and that decline in cerebral energy consumption is the passive result of decreased ATP utilization and is seen only when the brain is electrically active. Dr. Kramer contended that these drugs also inhibit oxidative phosphorylation, although to a lesser degree, and on that account may be unsuited to experiments investigating cerebral energy metabolism which in turn would be linked with the human condition. Dr. Kramer concluded by issuing a word of caution with respect to the concept of cerebral protection during anoxic or ischemic injury — protection through the use of drugs such as barbiturates. He pointed out that only hypothermia of the various interventions mentioned can be expected to retard spontaneous macromolecular degradation and is thus properly to be considered as truly protective of the brain as a whole during an ischemic insult.

Dr. Sundt continued the discussion by describing the method he had used in making NADH recordings in vivo, directed toward the analysis of incomplete focal cerebral ischemia. He mentioned that one of the major problems in using NADH recordings over a long period of time (hours rather than minutes) is the photodecomposition which occurs if too strong an incident light is used. In Dr. Sundt’s laboratory, a 100-watt mercury light source has solved the problem.

Dr. Bo K. Siesjo (Director of Research, E-Blocket University Hospital, Lund, Sweden) continued the discussion about the problems of brain hypoxia and brain ischemia. He pointed to a series of laboratory observations which suggest that if it is possible to perfuse all of the capillaries in brain tissue, the critical venous oxygen tension is well below 10 mm Hg. However, if the ischemia is induced by decreasing the mean arterial blood pressure, changes in ATP, ADP, and AMP occur at approximately 40 to 50 mm Hg in mean arterial blood pressure. Under such circumstances, the venous oxygen tension is approximately 25 mm Hg rather than 10 mm Hg. Dr. Siesjo went on to comment about the arterial hypoxia associated with severe anemia. He pointed out that reducing the hemoglobin concentration in the blood to 5 or 6 gm % is associated with an increase in blood flow of about three times normal, but there is no decrease in the venous oxygen tension. This raises such questions as: What triggers glycolysis in hypoxia and what mechanisms lead to an increase in the blood flow under anemic conditions? Dr. Siesjo placed emphasis on the fact that ischemia itself is not a homogeneous phenomenon; there are often well-perfused areas simultaneously with the presence of badly perfused areas or areas receiving no perfusion at all.
Dr. Richard J. Wurtman (Professor of Endocrinology and Metabolism, Massachusetts Institute of Technology, Cambridge, Massachusetts) was invited to make comments about catecholamines and reviewed the relationship of these substances to blood flow and vascular activity in the brain. He pointed out that there is a localization of monoaminergic neurons in the rat brain. The noradrenergic neurons have their cell bodies fairly far down in the brain stem. These cells send axons upward, either by the medial forebrain bundle or from the locus ceruleus by a dorsal bundle and also send axons down the spinal cord. Serotonergic neurons are next while dopaminergic neurons have their cell bodies located only high in the brain stem. He added that one could imagine that if a vascular lesion affected predominantly the dopaminergic portion of the brain stem, its chemical effects on dopamine would be a lot greater than on norepinephrine or serotonin. Dr. Wurtman went on to describe experiments done in collaboration with Dr. Nicholas T. Zervas (Associate Professor of Surgery, Harvard Medical School, Boston, Massachusetts); experiments designed to study the effects of specific vascular lesions on the levels and metabolic turnover of monoamines in the brain. It was noted that there was a reduction of dopamine within dopaminergic neurons that had been damaged by the induced ischemia, but there was no reduction of dopamine within noradrenergic neurons. He went on to suggest that in Dr. Kogure’s experiments the changes in dopamine observed are probably taking place within noradrenergic neurons. He suggested two possible explanations: (1) an increased activity of these neurons is causing an increased release of norepinephrine and a consequent increased synthesis of catechols, and (2) there was enough anoxia or hypoxia in the entire cortex so that dopamine beta oxidation, the step that converts dopamine to norepinephrine, was not proceeding at the same rate that it would in the intact animal. Dr. Wurtman summarized his observations and suggested that the very major release of stored dopamine within dopaminergic areas might be harmful since the dopamine probably is not metabolized normally. If large amounts of dopamine, thus released, interact with dopaminergic receptors and also leak out from synaptic areas to interact with blood vessels, general damage might result. In addition, in the animal with chronic cerebral infarction the selective decrease of the population of dopaminergic neurons might result in a kind of parkinsonism-like picture.

Dr. Donald B. Tower (Acting Director, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland) continued the discussion by pointing out that one of the most important changes occurring when blood supply is interrupted is the leak of potassium out of the cells. One of the most important results of this potassium leak is edema. The edema, both in vitro and in vivo, seems to be clearly localized to the astrocytes. The astrocytes contain a complex system which is probably very important to the modulation of fluid in ionic environment in the brain. The astrocyte contains a potassium-dependent inward transport of chloride and a majority of the carbonic anhydrase activity in the brain, as well as bicarbonate activated ATPase. When potassium leaks out of the nerve cell, fluid and electrolyte imbalance occurs and the astrocytes begin to swell. Dr. Tower emphasized that in the experimental animal reduction of the chloride level is associated with improvement in the edema and that administration of Diamox can aid in preventing edema. He went on to point out that within cells there are very important compartments — studies need to be done concerning the synaptic complex and the postsynaptic effector, as there may be changes at these sites which cannot be identified by examining whole tissue or even whole cell preparations. Dr. Tower pointed out that he did not agree with Dr. Michenfelder that after decapitation all effects of anesthetics are abolished. Effects on acetylcholine stores and on the stores of glutamic acid persist in anesthetized animals as contrasted with unanesthetized animals after decapitation.

This portion of the program was completed with a series of questions and speculative hypotheses which added no more information about how to prevent cerebral ischemia or alleviate it after it occurs.

The next portion of the Conference was under the general title “Effects of Reduction of Energy State.” Dr. Frank M. Yatsu (Associate Professor of Neurology, University of California School of Medicine, San Francisco, California) first spoke on “Lipid Metabolism.” He has noted that ischemic synaptosomes synthesize reduced quantities of phosphatidic acid and inositol glycerophosphatide. The findings suggest that neurotransmission may be a vulnerable focus of ischemic injury and warrant further investigation. Identification of a vulnerable focus to ischemia can provide a marker for the evaluation of pharmacological agents aimed at preserving or stabilizing these functions during varying degrees of ischemic insult. He had found that irreversible ischemic damage can be averted in his model of ischemia by the administration of barbiturates after the onset of the isoelectric EEG.

The next presentation was by Dr. Takehiko Yanagihara (Assistant Professor of Neurology, Mayo Medical School, Rochester, Minnesota) and concerned “Protein and Nucleic Acid Metabolism.” He talked about investigations aimed at looking at the metabolism of protein in ribonucleic acid to see whether their neuronal or the glial elements are more involved in cerebral anoxia. Dr. Yanagihara has developed a model of cerebral anoxia in which normal rabbit brains were obtained following brief transcardiac perfusion with ice-cold Ringer’s solution. Subse-
quently, the experimental material was kept on oxygen. The incubation was continued for from five minutes to 30 minutes. Dr. Yanagihara went on to describe in detail the inhibition of protein synthesis occurring following the anoxia. Subsequently, the protein synthesis was carried out with isolated microsomal fractions. He described the effects produced by anoxia (from five minutes to 30 minutes) in four different groups.

Discussion was opened by Dr. J. Norman Allen (Professor of Neurology, Ohio State University College of Medicine, Columbus, Ohio), who interpreted in summary fashion some of the observations made by Drs. Yatsu and Yanagihara.

In open discussion Dr. Arthur G. Waltz (Professor of Neurology, University of Minnesota School of Medicine, Minneapolis, Minnesota) emphasized that Dr. Allen had brought up the matter of the "bloodless brain" and the no-reflow phenomenon. He added that blood in the brain seems to be important and reminded the conferees of work done at the Max Planck Institute (Cologne, Federal Republic of Germany) where Dr. K. A. Hossmann found recovery after one hour of ischemia if there was no blood in the brain, but no recovery if there was blood in the brain.

The session was concluded with a variety of questions but no answers of current clinical significance.

The next session of the Conference was opened by Dr. Jewell L. Osterholm (Professor of Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania), who presented "Effects of Ischemia on Neural Transmitters." Dr. Osterholm described his experiences with a spinal cord injury model. Among other things mentioned was that microvascular arrest (posttraumatic) in the spinal cord may result from an excessive and perverted activity of an autoregulatory bulbospinal noradrenergic system. This bulbospinal system, if it exists at all, might account for failure of neurotransmitters to leak from their normal storage and flood the surrounding area, perhaps interacting with the vascular smooth muscle and producing more feedback. Dr. Zervas mentioned that this dual system, if it exists at all, might account for failure of collateral circulation in progressing stroke.

Dr. Waltz related that he has measured norepinephrine after occlusion of the middle cerebral artery in cats. The changes are different at different times after ischemia and are bilateral. Comparing the occluded and nonoccluded sides, he did not find an increase in norepinephrine consistently in the ischemic side; that is, when necrosis had occurred after many hours and up to seven days, there was less norepinephrine in the necrotic area than in the ischemic zone.

Dr. Waltz admonished the conferees that catecholamine assays are not easy; samples should be sent off double-blind to another investigator working in the field to check laboratory results. He added that there are great variations among species and brain catecholamine levels and, even more significantly, great variation in the utility of species for this type of experiment because of the extent of inbreeding. In addition, there will be variations from species to species in the distribution of middle cerebral blood.

Dr. Wurtman reminded the conferees that he had reported last year that the administration of norepinephrine or catecholamine synthesis inhibitor, namely alpha methyltyrosine, prevented or extended the survival time or the actual survival of squirrel monkeys which had temporary ligation of the middle cerebral artery. Together with Dr. Wurtman, the hypothesis was developed that vessel spasm or local ischemia, resulting in damage to blood vessels, permits the release of whatever vasoactive substances are carried in the blood. These diffuse into an injured area, interact with the vascular smooth muscle, feed back and cause more ischemia and more damage to the blood vessel, and lead probably to hemorrhagic infarction. At the same time, the ischemic insult with damage to axons and nerve terminals permits monoamine neurotransmitters to leak from their normal storage areas and flood the surrounding area, perhaps interacting with the vascular smooth muscle and producing more feedback. Dr. Zervas mentioned that this dual system, if it exists at all, might account for failure of collateral circulation in progressing stroke.

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Dr. John Stirling Meyer (Professor of Neurology, Baylor College of Medicine, Texas Medical Center, Houston, Texas) mentioned that in acute stroke patients the cyclic AMP is increased in cerebral venous blood and cerebral spinal fluid and norepinephrine and serotonin are increased; these can
be correlated with the reduction of cerebral blood flow in the state of the disordered metabolism and that these disorders and their vascular blood flow metabolic effects can be improved by phenoxybenzamine or glycerol.

After considerable discussion and many speculations by many different people, Dr. Siesjo said "no one knows why there is an increased rate of glycolysis in hypoxia!"

The final topic of the Conference, "Morphological Changes Associated With Metabolic Abnormalities," was addressed initially by Dr. Julio H. Garcia (Professor of Pathology, University of Maryland School of Medicine, Baltimore, Maryland). He summarized a presentation of visual evidence by saying that in the cat at the ultrastructural level, after occluding the middle cerebral artery, no changes are noted prior to 15 minutes. Subsequent to this time only a fraction of the neurons are involved. Some of the changes he observed he believes may be reversible.

Dr. John Moossy (Professor of Pathology and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania) summarized a variety of changes occurring in global cerebral ischemia. He pointed out that in focal perfusion failure in the territory of a single artery there is often partial cerebral ischemia. In this type of ischemia, neuronal injury may occur and be reversible or irreversible. He reemphasized the patchy effect of partial cerebral ischemia; that in zones of obvious infarction some neurons may be spared. He restated that there is general agreement among all investigators that mitochondrial changes, limited to neurons, are among the earliest alterations, although there are differences of opinion about the nature and significance of these changes.

In the open discussion, Dr. G. F. Molinari (Section on Head Injuries and Stroke, Collaborative and Field Research, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland) reported that in a preliminary study, segmental occlusion produced by an intrinsic embolism of the middle cerebral artery produced infarction in all animals independent of the use of barbiturate agents before or after the procedure.

Subsequently, there was a further description by Drs. Moossy and Garcia of some of the earliest changes that affect capillaries — changes associated with ischemia. Dr. Garcia commented that the disappearance of synaptic vesicles is always very late as the vesicles appear to be resistant to the autolysis produced by global cerebral ischemia. However, the postsynaptic portion of the synapse becomes markedly enlarged very early, within five minutes after the onset of ischemia.

Dr. Whisnant then adjourned the Conference.
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