Third Joint Meeting on Stroke and Cerebral Circulation

Fairmont Hotel, New Orleans, Louisiana
February 16-18, 1978

Sponsored by

STROKE COUNCIL
American Heart Association

CEREBROVASCULAR SURGERY SECTION
American Association of Neurological Surgeons

CANADIAN STROKE SOCIETY
Canadian Heart Association

THE SOCIETY FOR VASCULAR SURGERY

Further information about registration ($60) and hotel may be obtained from Mr. Dale Stringfellow, American Heart Association, 7320 Greenville Avenue, Dallas, Texas 75231. Registration is also available at the meeting. This continuing medical education offering meets the criteria for 11 hours of credit in Category I for the "Physician's Recognition Award of the American Medical Association."
SESSION I

Thursday (3:00 to 4:00 p.m.)
3 p.m. Registration, Fairmont Hotel
4 p.m. Welcome — Robert G. Siekert

Thursday (4:00 to 7:00 p.m.)
Symposium
Non-Invasive Techniques: Value in Carotid Artery Disease.
James T. Robertson, Chairman. Participants: William Gee, Merrill P. Spencer, Robert H. Ackerman, Burton A. Sandok.

Lecture
Atherosclerosis — New Directions. Russell Ross.

SESSION II: CLINICAL ASPECTS I

Friday (8:00 to 9:45 a.m.)

II-1
Stroke With Atrial Fibrillation — Fisher CM
(Massachusetts General Hospital, Boston, Massachusetts)

Of 100 unselected cases of atrial fibrillation (AF), from hospital records, embolism occurred in 35. In 30 cases the brain was involved first and in 5 the legs, i.e., in 86% of cases the first symptomatic embolus went to the brain. The brain should receive only 1/5 of cardiac emboli if distribution paralleled blood flow. Seventeen of 48 patients (35%) suffered a stroke within 4 years of the diagnosis of AF. AF is a strong risk factor for stroke.

In another series of 100 consecutive well-studied, embolic stroke cases with AF, in 70 either death or a severe deficit resulted. About 2/3 of the patients were over 70. Prestroke health was good in 90. AF was persistent in 63, paroxysmal in 37. In 83 cases heart disease was nonvalvular, in 17 valvular. Of 109 embolic episodes, 91 involved the middle cerebral territory (51 left, 40 right), 17 vertebral-basilar and 1 anterior cerebral. Only 1 stroke began with a convulsion. Seizures may occur without a recognized stroke. There was a history of prior embolism elsewhere in the body in only 2 cases. The known duration of AF before embolism was less than 4 years in 53%. A second episode occurred in 11 patients, 3 within 10 days. Prevention of cerebral embolism with anticoagulant therapy is an important goal.

II-2
Acute Cerebellar Infarction — A Surgical Emergency — Feely MP, Dempsey PJ (University of South Alabama, Mobile, Alabama)

The presentation of an 18-year-old girl in deep coma, as a result of acute infarction of the left cerebellar hemisphere, prompted our review of the literature on this condition. We have found 16 other cases reported and discuss the clinical features of 17 cases of acute cerebellar infarction. The 3 of 17 patients that were not treated surgically all died. Of the 14 treated surgically 10 survived the operation and 4 of these made an eventual complete recovery.

The diagnosis in our case was made on the computerized tomographic (CT) scan. A search shows that this is the first reported case of cerebellar infarction to be evaluated by CT scan. The following features were noted on the scan, which was performed 36 hours after the onset of symptoms:

(1) The left cerebellar hemisphere was reduced in density, and did not enhance with contrast injection. (2) The 4th ventricle was not displaced. (3) There was mild enlargement of the lateral ventricles suggestive of early hydrocephalus.

These findings are in keeping with the usual CT scan appearance of cerebellar infarction.

The etiology of this lesion and the role of brainstem compression in the clinical features are briefly discussed.

II-3
Effect of Progressive Ischemic Stroke on Plasma Catecholamines — Jallad MS, Weidler DJ, Das SK
(University of Michigan Medical Center, Ann Arbor, Michigan)

The effect of progressive ischemic stroke induced by sequential occlusion of the left vertebral and the left carotid arteries on dopamine (D), epinephrine (E), and norepinephrine (NE) concentrations in 10 unanesthetized cats was determined. After left vertebral occlusion, there was a significant increase (concentrations in Pg/ml) in D from 55 ± 47 to 77 ± 48, E 165 ± 100 to 338 ± 209, NE from 1156 ± 989 to 1312 ± 1128. Cardiac output (CO) and heart rate increased. With progressive ischemia after left carotid occlusion, there was further significant increase in D 775 ± 486, E 2010 ± 1975, NE 3190 ± 1975. However, CO and heart rate decreased. Complete heart block ensued in all surviving cats. Thus, altered cardiac function may be mediated by an increase in plasma catecholamines following the onset of ischemic stroke. The bradycardia and heart block that was observed following further ischemic insult were unexplained, but could be ascribed to parasympathetic predominance.

II-4
Monocyte Cholesterol Ester Hydrolase (CEH) in Menstruating Women: Possible Role in Atherosclerosis — Yatsu FM, Hagemenas FC
(University of Oregon Health Sciences Center, Portland, Oregon)

Atherosclerosis, the primary cause of strokes is of uncertain etiology though clearly multifactorial. The possible contribution of CEH deficiency, postulated by deDuve, is supported by our finding of significantly reduced CEH in both atherosclerotic arteries and in monocytes of patients undergoing endarterectomy. Since premenopausal women are protected against atherosclerosis, we investigated serially, every 5-day, monocyte CEH activities in 6 women. One-1.5 million monocytes were incubated with acetone-dispersed, labeled cholesterol; and cholesterol and its ester were extracted and counted by liquid scintillation. Results show a significant cycling of CEH activity from day 5 to 20 (1377 ± 308 to 2139 ± 243 pmoles/mg protein/hr, p < 0.05). Two lysosomal enzymes, β-D-N-Acetylglucosaminidase and β-D-glucuronidase showed no significant alterations.

Our results showing cyclic changes in monocyte CEH in women, while 2 marker lysosomal enzymes remain unchanged, suggest a possible relationship between the cycling CEH activity and its effect on cholesterol-ester metabolism, a significant factor in atherogenesis. We postulate that the known protection of premenopausal women against atherosclerosis is in part mediated by a generalized cyclic activity of CEH.

From 1955 through 1976 86 cases of primary intracerebral hemorrhage occurred in Rochester, Minnesota. The location of the hemorrhage was: hemispheric 77%, cerebellar 15%, pontine 7%; midbrain 1%. Mean age of onset was 70 with a 1:1 male:female ratio. The one-month survival rate was 15%. Hypertension as defined by a mean pre-hemorrhage blood pressure ≥160/90 and/or heart weight exceeding 400 grams on postmortem was present in 76%. 24% were on long-term anticoagulant therapy but only 2 patients were above the therapeutic range at onset. When a history was obtainable, onset was abrupt in 83%. 42% were comatose on admission and only 8% fully alert. Headache was present in 67% and nuchal rigidity in 25%. Papilledema, subhyaloid hemorrhages, and seizures were rare. When examined, the spinal fluid was grossly bloody in 82%. Computerized tomography was performed on 8 patients and demonstrated an area of increased attenuation, often with mass effect, even when done less than 24 hours after onset. Autopsy rate was 83%. Cerebral edema, herniation, and secondary brainstem hemorrhages were common. 27% had an old infarction on postmortem and 10% an old hemorrhage.

Strokes With Head Injury — Blau AM, Richardson JC (Hospital & Rehabilitation Centre, Toronto, Ontario)

This clinical study considers the nature and implications of occlusive and hemorrhagic cerebrovascular accidents which have been caused to a major or minor degree by head trauma. Our clinic has extensive experience and facilities for assessment of brain injured workmen at later stages.

During the five-year period 1972-1976 a series of 431 head injuries, chiefly blunt ones, was reviewed. Aside from the vast majority with obvious direct traumatic parenchymal damage there were 22 which might be classed as strokes related to trauma. There were 4 examples of pre-existing saccular aneurysms rupturing after trauma. In one case delayed intracerebral hemorrhage after head injury was explained by an arteriovenous malformation. Aside from the frequent occurrence of intracerebral hemorrhage concurrent with surface contusions and meningeal hemorrhage, there was a smaller group of 8 with purely intracerebral hematomas. There were 9 occlusive arterial cerebral infarctions, 7 internal carotid, 1 middle cerebral and 1 vertebralbasilar.

A cerebral vascular accident after head injury may be immediate or delayed and may be largely or only minimally caused by the trauma. Appraisal of these factors has been improved by modern neuroradiological and neurosurgical management.

The Declining Incidence of Stroke: The Framingham Study — Wolf PA, Dawber TR, Thomas HE Jr, Colton T, Nickerson R, Pool J (Boston University School of Medicine, Boston, Massachusetts)

Death rates from cerebrovascular disease have been declining over the past 50 years in most countries; the decrease is more marked in women. Has there been a fall in stroke incidence or are trends in mortality due to diagnostic or death certificate coding practices?

The stroke incidence rate for men and women age 50 to 61 in the first 12 years of a 24-year study was compared with that of the same age group in the second 12 years in the population sample at Framingham, Massachusetts. Stroke incidence is indeed lower in women in the later period. Women have less of a rise in blood pressure, greater use of anti-hypertensives, and less weight gain than men and this corresponds to a lower incidence of stroke. Blood pressure was higher in women than in men above age 48 in the early years of the study. In later years the blood pressure in women was lower than in men at all ages. Differences between longitudinal and cross-sectional trends in blood pressure in the two sexes are striking and correlate with trends in stroke incidence.


To determine whether detection and treatment of TIA in elderly population groups would significantly reduce the occurrence of completed strokes, a survey of TIA was undertaken in a free-living community of 17,000 retired white men and women in southern California. The present paper describes the use of a mailed self-addressed questionnaire for detection of TIA and its validation by neurologic interview. Subsequent reports describe the results of long-term follow-up observation. TIA questionnaires were mailed to each person in the community and, within a period of less than 5 months, responses were obtained from 11,000 persons, or 63% of the community. Approximately 7% were considered to have probable TIA on the basis of a history of transient motor, sensory, visual or speech disturbances in the previous year. Neurologic interviews were then carried out in 1,500 persons comprising all persons with probable TIA and a sample of the remaining persons to determine the validity of the reported symptoms. About 10% of those interviewed were found to have cervical bruises and 30% had elevation of blood pressure. When final tabulations are completed, it is estimated that the incidence of TIA in this community will be slightly more than 8/1000/year.

Regression of Primate Carotid Artery Atherosclerosis at 200 vs 300 mg/dl Plasma Cholesterol Concentration — Bond MG, Bullock BC, Lehrer NDM, Clarkson TB (Bowman Gray School of Medicine, Winston-Salem, North Carolina)

To determine if common carotid artery atherosclerosis could be regressed, 54 male rhesus monkeys were first fed an atherogenic diet containing 1 mg cholesterol/Cal for 19 mos. After atherosclerosis induction the animals were divided into 3 equal groups. Gp IA was killed at the end of the 19 mos for gross evaluation of carotid artery atherosclerosis. By adjusting dietary cholesterol the remaining animals were maintained at plasma cholesterol concentrations of either 280–320 mg/dl (Gp IB,) or 180–220 mg/dl
(Gp IC₃) for 24 mos. At necropsy the right common carotid artery was opened, fixed flat in formalin and stained with Sudan IV. The % of intimal surface containing fatty streak (FS), diffuse intimal thickening (DIT), fatty plaque (FAP) and fibrous plaque (FP) was estimated by two observers. Results were (Mean ± se).

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<tr>
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<th>FS</th>
<th>DIT</th>
<th>FAP</th>
<th>FP</th>
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<tbody>
<tr>
<td>Gp IC₃</td>
<td>15 ± 5.4</td>
<td>38 ± 7.3</td>
<td>8 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>p IB₄</td>
<td>15 ± 3.3</td>
<td>14 ± 4.2</td>
<td>9 ± 2.4</td>
<td>18 ± 5.8</td>
</tr>
<tr>
<td>Gp IC₃</td>
<td>± 0.9*</td>
<td>9 ± 4.7*</td>
<td>0*</td>
<td>10 ± 3.3</td>
</tr>
</tbody>
</table>

*IB₄ vs IC₃ significantly different at p < 0.025. Lowering of plasma cholesterol concentration by 100 mg/dl for 24 mos resulted in less extensive FS and FAP, but in more DIT. There was a tendency for less FP in IC₃ animals.

**II-10**


Regional cerebral blood flow (rCBF) was repeatedly measured by a hydrogen clearance method in the cortex of our new animal models. These are stroke-prone spontaneously hypertensive rats (SHRSP) which developed stroke spontaneously in a high incidence of more than 90%, and arterioliposis-prone rats (ALR, Yamori, 1976) which developed quickly cerebrovascular fat deposition when fed on a hypercholesterolemic diet. Controls were stroke-resistant SHR (SHR-SR), which showed a low incidence (less than 10%) of stroke in spite of the development of hypertension, and Wistar-Kyoto rats (WK), from which SHR and ALR were derived.

When SHRSP developed severe hypertension (over 200 mmHg) around the age of 2 months, rCBF began to decrease abruptly. Contrarily, such a reduction in rCBF was not noted in either SHR-SR or WK. Chemical cerebrovascular reactivity markedly decreased in SHRSP at the age of 9 months around the time when male SHRSP developed a stroke. On the other hand, anti hypertensive agent-treated SHR-SR developed no stroke and maintained a normal range of rCBF as well as untreated SHR-SR and WK.

**SESSION III: EXPERIMENTAL CEREBRAL ISCHEMIA**

**Friday (10:15 a.m.-12:15 p.m.)**

**III-1**

Effect of Glucose Infusion on the Brain's Response to Diffuse Ischemia — Ginsberg MD, Welsh FA, Budd WW (University of Pennsylvania, Philadelphia, Pennsylvania)

Using a reproducible model of severe cerebral ischemia in the pentobarbital-anesthetized cat (basilar and bilateral carotid artery occlusion and mild hypotension), we studied the effect of preischemic glucose infusion upon local cerebral blood flow (ICBF), regional brain metabolites, and brain water content following ischemia and 90 min of post-ischemic recirculation. In this model, 15 or 30-min of ischemia led to virtually absent hemispherical ICBF, severely depressed brain phosphocreatine and ATP levels, and greatly elevated lactate. In non-glucose-infused animals, recirculation after 15 min of ischemia produced uniform recovery of ICBF to 31-35% of control, 72-83% recovery of brain ATP, and declines in lactate; recovery from 30 min of ischemia led to CBF heterogeneities, with zones of persistent ischemia and metabolic failure. With IV infusion of 1.5 gm/kg of glucose solution 1 hr prior to a 30 min period of ischemia, brains remained virtually totally ischemic during recovery, regional brain metabolites and glucose utilization were markedly deranged, and there was generalized swelling. Preischemic glucose also altered the sequelae of a 15-min insult, producing in several cats a persistent no-flow state. Brain water content was elevated in both infused and non-infused animals. The mechanism of the glucose effect appears to lie in a dramatic impairment of postischemic cerebral perfusion.

**III-2**

Effects of Hypercapnia on Cerebral Oxygen and Glucose Consumption in the Conscious Rat — DesRosiers MH, Kennedy C, Sakurada O, Shinohara M, Sokoloff L (NIMH, Bethesda, Maryland)

Recent studies have suggested that CO₂ reduces cerebral glucose consumption (CMRG) without significantly altering cerebral oxygen consumption (CMRO₂). To elucidate this discrepancy, two series of experiments were conducted in conscious Sprague-Dawley rats breathing 5% CO₂ in air. In a first series, local cerebral glucose utilization (LCGU) was measured by means of the [¹⁴C] deoxyglucose method. In a second series, CMRG and CMRO₂ were measured with a modification of the Kety-Schmidt method. In the first series, CO₂ produced a marked and uniform reduction in LCGU in all 33 structures examined. This reduction averaged 32% in grey structures (69 vs. 101 µmoles/100 g/min for control rats), and 37% in white structures (24 vs. 38 µmoles/100 g/min). In the second series, there was a 54% decrease in CMRG (39 vs. 85 µmoles/100 g/min), associated with a 30% fall in CMRO₂ (6.29 vs. 9.03 ml/100 g/min). These results show that hypercapnia, even when moderate, homogeneously inhibits glucose consumption throughout the brain, and further suggest a concomitant stoichiometric decrease in oxygen consumption. They do not support the possible utilization of substrates other than glucose by brain for the maintenance of a normal energy expenditure during hypercapnia.

**III-3**

Glycolytic Metabolism of Isolated Cerebral Microvessels — Chan MY, MacMillan VH (University of Toronto, Toronto, Ontario)

In order to assess the process of endothelial glycolysis, capillaries were isolated from cerebral cortex of rats using differential gradient centrifugation and passage through a column of glass micro-beads, with subsequent measurement of marker enzymes, anaerobic lactate production and activity of selected glycolytic enzymes. Microscopic examination of microvessel fractions revealed well preserved capillary structures which were essentially free of adherent glial cells. A 10-14 x enrichment of the endothelial marker
enzyme γ-glutamyl transpeptidase supported the observed microscopic purity of the preparations. Capillaries incubated in 95% N₂-5% CO₂ produced lactate at 30% of the rate of cortical tissue. The relatively lower glycolytic capacity of capillaries was further indicated by the lesser activities of phosphorylase (10%), hexokinase (11%), phosphoglucomutase (17%), phosphohexoseisomerase (20%), lactate dehydrogenase (33%) and glucose-6-P dehydrogenase (31%). Since the magnitude of intracellular lactate accumulation in anoxia-ischemia has been implicated in the pathogenesis of the cellular damage, this lesser glycolytic capacity may in part explain the suggested higher resistance of capillaries to anoxia-ischemia.

III-4

Cerebral Blood Flow and Metabolism During Neonatal Hypoglycemia — Salcedo A, Hernández MJ, Vannucci RC, Brennan RW (Hershey Medical Center, Hershey, Pennsylvania)

Low blood sugar concentrations are frequently encountered in the neonatal period. However, the effects of hypoglycemia on cerebral blood flow (CBF) and metabolism in newborns are poorly understood. A modification of the Kety and Schmidt technique employing 18O₂ was used to measure CBF and cerebral metabolic rates (CMR) during normoglycemia (N) and hypoglycemia (H) in paralyzed newborn dogs passively ventilated with 70% N₂O-30% O₂.

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>CBF</th>
<th>CMR O₂</th>
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<tr>
<td>(mM/1)</td>
<td>(ml/min/100 gm)</td>
<td>(mlO₂/min/100 gm)</td>
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<tr>
<td>N 8.58 ± 2.10</td>
<td>23 ± 8</td>
<td>1.15 ± 0.25</td>
</tr>
<tr>
<td>H 0.69 ± 0.03</td>
<td>22 ± 4</td>
<td>0.90 ± 0.08</td>
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<tr>
<td>p &lt; 0.001</td>
<td>N.S.</td>
<td>N.S.</td>
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Thus, CBF and CMR O₂ were unchanged, despite a marked decline in blood glucose. Mean CMR glucose decreased from 7.24 ± 3.80 to 4.05 ± 0.68 μmoles/min/100 gm, while CMR lactate in brain rose from 1.82 ± 2.06 to 8.98 ± 2.56 μmoles/min/100 gm, exceeding glucose as the dominant cerebral energy fuel. These findings support the concept that cerebral energy fuel. These findings support the concept that glucose transport into the brain is oxygen dependent since a reduction of 2-deoxy-D-glucose (2-DG) glucose entry into the cerebral capillaries was observed in microvessels separated from ischemic brain and from normal capillaries exposed to anoxia in vitro. The purpose of this investigation has been to evaluate the effect of ischemia and anoxia on the capillary uptake of amino acids which are supposed to be actively transported across the blood brain barrier (BBB).

The capillary uptake of the labeled isoleucine, cycloleucine, phenylalanine and glutamine was saturable and was found to be increased except for glutamine in cerebral capillaries isolated from brains of gerbils with bilateral carotid artery occlusion for 3 minutes. This uptake decreased progressively from 1–30 minutes after reestablishment of cerebral blood flow. Moreover, the capillary uptake of these amino acids was not affected by oxygen and/or NaCl deprivation in vitro, suggesting that the entry of the tested neutral amino acids into the cerebral capillaries is a carrier mediated process but oxygen and Na-independent.

Therefore the passage of these substrates across the BBB most likely has the same mechanism and was not decreased in ischemia.

III-5

The Significance of 5′Nucleotidase in Ischemic Brain — Kogure K, Lee R, Traviesa D (University of Miami, Miami, Florida)

Increased activity of cerebral 5′nucleotidase may contribute to ischemic brain injury by causing depletion of the adenylate pool and accumulation of adenosine, thereby activating adenylyl cyclase and producing a rise in intracellular cAMP, a mediator of energy dependent reactions.

Ischemic tissue products, H⁺, lactate, NH₄⁺, inorganic phosphate as well as theophylline and ATP were shown to inhibit 5′nucleotidase in vitro. The purpose of this study was to determine: 1) whether ischemic tissue products can counteract the decline in ATP and thereby inhibit cerebral 5′nucleotidase; 2) whether pharmacologic alteration of 5′nucleotidase activity can be accomplished in ischemic brain.

Total brain ischemia was produced in Wistar rats (250–400 gms) by decapitation. One-half of the animals received theophylline 100 mg/kg, 30 minutes prior to the onset of ischemia. Heads were incubated at 37°C for 0, 15, 30 and 60 min and then frozen by the transcalvarial application of liquid nitrogen. Supernatant of brain homogenates was assayed for total protein and 5′nucleotidase activity by a colorimetric method.

Activation of 5′nucleotidase at 15 min of total ischemia was followed by a fall in activity. ATP depletion appears to overcome the inhibitory effect of ischemic tissue products. Theophylline retards the activation.

III-6

Ischemic and Anoxic Uptake of Neutral Amino Acids Into the Isolated Cerebral Capillaries — Micic D, Klatzo I, Spatz M (NINCDS), National Institutes of Health, Bethesda, Maryland

Recent studies suggested that glucose transport into the brain is oxygen dependent since a reduction of 2-deoxy-D-glucose (2-DG) glucose entry into the cerebral capillaries was observed in microvessels separated from ischemic brain and from normal capillaries exposed to anoxia in vitro. The purpose of this investigation has been to evaluate the effect of ischemia and anoxia on the capillary uptake of amino acids which are supposed to be actively transported across the blood brain barrier (BBB).

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III-7

Failure of Pentothal to Protect from Anoxic Cerebral Injury — Snyder BD, Ramirez-Lassepas M, Sukhum P (St. Paul Ramsey Hospital, St. Paul, Minnesota)

To corroborate thiopental protection from cerebral anoxia after cardiorespiratory arrest, 23 sedated, curarized, adult dogs were asphyxiated by plugging the endotracheal tube. EEG, ECG and BP were monitored. Electrocortical silence (ECS) was seen 2–4 minutes after asphyxia, coinciding with drop in BP. Cardiac arrest occurred 3–4 min after ECS. Cardiopulmonary resuscitation (CPR) was started 7 minutes after ECS. Closed chest compression, artificial respiration and intravenous administration of standard drugs restored effective cardiac function in 1–3 minutes in all dogs. Twelve received no other treatment (controls), 10 of them regained consciousness and spontaneous respirations, but
remained decerebrate, blind, unable to drink or feed. Survival was an average of 2½ days. Two dogs returned to a normal neurologic state. Eleven dogs were treated with thiopental after CPR, 7 received 15 mgm per kilo in the first minute, followed by 23 mgm per kilo over one hour; 4 received 60 mgm per kilo in the first 5 minutes, followed by 30 mgm per "kilo over 1 hour. Except for 1 dog in the low-dose group that recovered neurologically, thiopental treated dogs showed no neurologic or survival improvement over the controls. The high dose group had worse survival time.

III-8

Treatment of Induced Cerebral Infarction in Rats with Levodopa or with Glycerol — Popovic P, Popovic V, Schaffer R, Sutton CH (Emory University School of Medicine, Atlanta, Georgia)

Study on 86 rats shows that administration of large amounts of levodopa did not bring improvement in survival of rats after acute cerebral infarction induced by injection of carbon microspheres. However, when 10% glycerol was used, the survival after cerebral infarction was significantly greater than in the control or in the levodopa treated rats. Combination of levodopa and glycerol therapy also significantly improved the survival of infarcted animals. It appears that glycerol alone is the main factor in eliciting this beneficial effect. Pathological findings (gross or microscopic) indicate striking changes in brain tissue after embolization. Brain tissue histology indicates that glycerol treated animals developed a less severe edema and had less tissue disruption than control animals. Development of brain edema of the infarcted left hemisphere corresponded to the type of treatment and to the length of animal survival. The results suggest that treatment of edema should be one of the primary steps in therapy after acute cerebral infarction.

III-9

Modification of Acute Focal Ischemia by Treatment with Mannitol — Little JR (Montreal Neurological Institute, Montreal, Quebec)

A simple implanted device was used to acutely occlude the left middle cerebral artery (MCA) of conscious adult cats. Half of the animals received no treatment and half were given mannitol (1.2 gm/kg IV) at the time of occlusion. The initial neurological findings in both groups were similar, that is, agitation, forced circling, and right hemiparesis. The treated cats remained alert but the untreated cats became lethargic and drowsy. Perfusion with a mixture of colloidal carbon and buffered paraformaldehyde was carried out from 30 minutes to 6 hours following MCA occlusion. The initial distribution and grade of the neuronal changes. A significant difference (p = 0.01) between the two groups was demonstrated. Measurement of capillary luminal diameters revealed progressive narrowing in the ischemic tissue of the untreated animals reaching a mean capillary diameter of 4.5 ± 1.0 μ after 6 hours of ischemia (control 6.5 ± 1.0 μ). Mean capillary diameter in the treated animals at 6 hours was 6.0 ± 1.0 μ. Results of this investigation suggested that mannitol had a protective effect upon cerebral tissue during the primary phase of acute focal ischemia.

III-10

Effect of Interference with CSF Dynamics on the Survival Rate of Mongolian Gerbils Subjected to Cerebral Ischemia — Smialek M, Spatz M, Klatzo I (NINCDS, National Institutes of Health, Bethesda, Maryland)

Searching for measures which could significantly influence the clinical course of an ischemic brain injury, a procedure has been discovered in a serendipitous way which remarkably reduced the mortality rate of gerbils subjected to bilateral occlusion of the common carotid artery for 15 minutes.

The survival rate in the control group of animals subjected to carotid occlusion only was approximately 35% in 1-month-long observations. On the other hand, gerbils which were subjected, in addition to carotid clipping, to CSF tapping from the cisterna magna and to intraperitoneal injection of 2 ml of distilled water showed approximately 85% survival rate. A beneficial effect on the survival rate (approximately 75%) was obtained also in gerbils which instead of cisternal tapping and distilled water received respectively 0.02 ml of Ringer solution injected intracranially and 2 ml of 5% glucose intraperitoneally. Injection of glucose alone at the time of carotid occlusion resulted in increased mortality (85%) when this group of animals was compared to that of gerbils which were subjected to ischemia only (65%).

III-11

Effects of Anticoagulants (A/C) on Experimental Septic Embolism — Foote RA, Reagan TJ, Sandok BA (Mayo Clinic, Rochester, Minnesota)

The effect of A/C on lesions caused by varying types of cerebral emboli was studied in 57 dogs. Pathologic and angiographic studies were performed to assess the resultant arterial and parenchymal lesions.

Emboli which caused little or no inflammatory response in the artery (12) produced areas of infarction, but were not associated with hemorrhagic infarcts (HI), subdural (SDH) or subarachnoid hemorrhage (SAH). Furthermore, treatment with A/C prior to embolization (9) did not change the character of the lesions. Although there was a trend for smaller infarcts with A/C, this was not statistically significant.

The use of emboli which caused arteritis (i.e. bacterial contamination or the presence of lead-chromate in embolus) (21) was associated with HI, focal SAH and acute SDH. Treatment with A/C (16) was associated with a further increase in the incidence of SDH.

Conclusion: In this model, non-inflammatory emboli produced infarction without hemorrhage and A/C did not increase the risk of hemorrhagic complication. The use of emboli capable of producing an arteritis was associated with hemorrhagic lesions and the use of A/C was accompanied by additional hemorrhagic change.
SESSION IV: CEREBRAL BLOOD FLOW AND METABOLISM

Friday (1:45-3:30 p.m.)

IV-1

Effects on Cerebral Autoregulation of Medullary Stimulation — MacKenzie ET, Mori M, Reis DJ (Cornell University Medical College, New York, New York)

We examined the effects on cerebral autoregulation of electrical stimulation of the localized vasopressor area of the dorsal medullary tegmentum which mediates tonic vasomotor tone, the cerebral ischemic and Cushing reflexes. Focal cortical blood flow was measured by H2 clearance in urethane-anesthetized, ventilated rabbits. Mean arterial pressure (MAP) was adjusted by either i.v. phenylephrine or graded hemorrhage. In 22 unstimulated rabbits the upper limit of autoregulation was 130-139 mmHg; in 6 rabbits medullary stimulation (50 Hz; normal 5X threshold for the pressor response) increased the upper limit to 160-169 mmHg (p < 0.001). Following bilateral cervical preganglionic sympathectomy (n = 7), autoregulation was completely lost; flow increased at every level of MAP > 60 mmHg. Spinal transection at C1, which abolished the pressor response, also resulted in a loss of autoregulation (n = 5). These findings suggest that: (a) autoregulation during brainstem stimulation is largely mediated by a concurrent excitation of cervical sympathetic nerves, and (b) the medullary vasomotor center contains a powerful vasodilator system, probably intrinsic, whose action may be masked by concomitant activation of the cervical sympathetic nerves.

IV-2

Reduction in Neostriatal Blood Flow after d-Amphetamine Administration or Electrical Stimulation of the Substantia Nigra — Lavyne MH, Koltun WA, Zervas NT, Wurtman RJ (Harvard Medical School and Massachusetts Institute of Technology, Boston, Massachusetts)

Local cerebral blood flow was measured in the caudate nuclei and, in some instances, other areas of rat and monkey brain utilizing the hydrogen clearance technique. Resting values to caudate blood flow in the unanesthetized rat were similar to those reported elsewhere, i.e., 69 ± 4 ml/min/100 gm. The administration of d-Amphetamine sulfate (0.5 mg/kg i.p.) to rats with chronically implanted caudate electrodes paralyzed with pancuronium bromide, and ventilated in order to maintain arterial pH, PCO2 and PO2 with physiological range, caused a reduction in caudate flow by a maximum of about 33%. After pretreatment with haloperidol (5.0 mg/kg, i.p.), a drug that blocks dopamine receptors, d-Amphetamine sulfate (1.5 mg/kg/p.o.) also reduced caudate, but not cortical, blood flow in unanesthetized monkeys. Electrical stimulation of the pars compacta of the substantia nigra reduced ipsilateral caudate flow by about 25% without affecting flow in the contralateral caudate in these unanesthetized monkeys. This effect was modified by varying the frequency and intensity of stimulation. These studies indicate that intraparenchymal dopamine release can modify local blood flow through the neostriatum.

IV-3

Ischemic Threshold of Regional Cerebrovascular Reactivity to Hypocapnia — Blauenstein UW, Wilson EM, Wills EL, Halsey JH Jr, Lilly DD (University of Alabama, Birmingham, Alabama)

The regional CO2-reactivity of indices for total flow (ml/min), normalized flow rate (ml/100g/min), and perfused tissue mass (g) was studied in 20 healthy subjects with the 133Xe inhalation method. Paco2 was altered by 5-7% CO2 inhalation or by voluntary hyperventilation. The regional cerebrovascular response curves for a Paco2-range from 20 to 60 torr were constructed from a total of 76 measurements for each of the three indices, using an a+x.exp fit (x = Paco2).

All response curves were curvilinear. Total flow decreased less than the normalized flow rate with reduction of Paco2 in the hypocapnic range. The index for perfused tissue mass, however, reached a minimum at a Paco2 of about 27 torr and increased with further reduction of Paco2.

The findings suggest a metabolic-ischemic threshold below which dissociation of the extra- and intraparenchymal vasodepressor response to progressive hypocapnia occurs. Below a Paco2 of about 27 torr intraparenchymal vasodilation appears to counteract pending tissue ischemia imposed by metabolically unstrained hypocapnic vasconstriction of the extraparenchymal vessels. This dissociation could be utilized to titrate ischemic thresholds in cerebrovascular occlusive disease and to determine the homeostatic reserve of brain circulation.

IV-4

Thresholds of Focal Cerebral Ischemia in Unanesthetized Monkeys — Jones TH, Morawetz RB, Ojemann RG, Fitzgibbon S, DeGirolami U, Crowell RM (Massachusetts General Hospital, Boston, Massachusetts)

To investigate the pathophysiology of ischemic stroke, we performed temporary middle cerebral artery (MCA) occlusion in unanesthetized monkeys. Twenty-four monkeys (Macaca irus) were studied. A trans-orbital snare ligature permitted reversible MCA occlusion of varying duration. Six implanted electrodes determined ICBF by hydrogen clearance. Blood pressure and blood gases were checked serially. Neuropathologic evaluation was carried out two weeks after ischemia.

In most monkeys, MCA occlusion caused immediate hemiparesis with fall of ICBF values below 25cc/100g/min. When residual ICBF values were above 12cc/100g/min, deocclusion at four hours led to good recovery with little or no infarction. When residual ICBF was less than 12cc/100g/min, deocclusion at 2-4 hours led to fatal hemorrhagic infarction. In a few monkeys, ICBF never fell below 25cc/100g/min and no deficits were observed.

In unanesthetized monkeys, ICBF appears to define thresholds for ischemia: below 25cc/100g/min irreversible deficits appear, and below 12cc/100g/min irreversible infarction develops after 2 hours. CBF thresholds might be helpful in predicting outcome in clinical strokes and selecting cases for revascularization.
Hypertension and Acute Focal Cerebral Ischemia — Hernández MJ, Brennan RW, White WJ, Brierley JB (Hershey Medical Center, Hershey, Pennsylvania)

Adult monkeys (M. fascicularis) fed an atherogenic diet which included 2% cholesterol developed systemic and cerebral atherosclerotic lesions within 18 months, while control monkeys receiving a standard laboratory diet did not. After 18 months, cerebral blood flow (CBF) was measured in both atherosclerotic and control animals by an arterial inflow method and by a modification of the Kety and Schmidt technique, employing $^{133}$Xe. Basal CBF and cerebral metabolic rate for oxygen values in atherosclerotic monkeys averaged $54 \pm 4$ ml/min/100 gm, and $3.18 \pm 0.36$ ml O$_2$/min/100 gm, respectively, values not significantly different from controls. Autoregulation of CBF was intact in both groups. However, responses to hypercarbia in atherosclerotic primates were impaired, averaging 0.44 ml/min/100 gm per mmHg change in arterial pCO$_2$, a value significantly lower than in the control group. At necropsy, the lesions present in the intra- and extra-cranial components of the cerebral vasculature were surveyed and correlated with impaired CO$_2$ responses. Our results suggest that cerebral vascular reactivity to CO$_2$ is greatly diminished early in the course of atherosclerotic cerebral vascular disease, and that both intra- and extra-cranial arterial lesions may underlie the findings.

Reactivity of Cerebral Blood Vessels after Carotid Ligation in the Gerbil — Rosenblum WJ (Medical College of Virginia, Richmond, Virginia)

In order to study cerebrovascular reactivity in infarcted gerbils, one must know the effect of carotid ligation without infarction. We ligated the right carotid artery of 217 gerbils. Ninety-six died within 24 hrs. In 77 of the survivors, only 9 of whom had infaracts, norepinephrine (1, 10 or 100 ug/ml) and 5% BaCl$_2$ were applied to the pial arterioles while monitoring vascular diameter with TV microscopy and an image splitter. Seventy-nine sham-operated animals were similarly examined. Studies were performed 24, 48, 72, 96 and 120 hrs after surgery.

Norepinephrine failed to constrict arterioles in 17 of the 77 ligated gerbils compared with 6 of 79 shams ($p < .03$). No difference in magnitude of constriction was found between the 2 groups. At 24, 48, and 72 hrs after ligation, BaCl$_2$, which constricted arterioles in virtually all gerbils, had a significantly greater effect on ligated gerbils than on shams. Constrictions were equal to $73 \pm 28$, $72 \pm 26$ and $73 \pm 26$% of baseline diameter compared with $41 \pm 16$, $51 \pm 26$ and $48 \pm 22$% in the shams ($p < .01$, .05 and .02). The significant differences between ligated and sham-operated gerbils were unrelated to the small number of infarcts in the ligated group, but may be related to smaller vessel size and lower intraluminal pressure in the affected gerbils.

Hypertension and Acute Focal Cerebral Ischemia — Hayakawa T, Waltz AG, Jacobson RL (Pacific Medical Center, San Francisco, California)

Hypertension is the most important risk factor for stroke in humans. The influences of preexisting chronic hypertension on infarction and edema in experimental models of acute focal cerebral ischemia have not been investigated previously. For this study, hypertension was produced in 8 cats by nephrectomy and wrapping the opposite kidney. Three to six months later 1 middle cerebral artery was exposed transorbitally and occluded, in these 8 cats and 8 others. Neurologic deficits, regional cerebral edema (wet weight = dry weight), endothelial dysfunction (brain: blood ratio 99mTc), and sizes of resulting infarcts were studied. The hypertensive cats (mean 182 mmHg ± 22 (SD)) had greater deficits (including more deaths), more edema, greater endothelial dysfunction, and larger infarcts than the control cats (134 mmHg ± 13). In this model of acute focal cerebral ischemia, preexisting hypertension predisposes to larger and more severe cerebral infarcts, presumably because of increases of ischemic cerebral edema resulting from changes in the cerebral endothelial barrier induced by the hypertension.

Role of Hypertension in the Microcirculatory Responses to Experimental Head Injury — Wci EP, Navari RM, Kontos HA, Patterson JL Jr (Medical College of Virginia, Richmond, Virginia)

We reported previously that experimental head injury produced sustained vasodilation of pial arterioles, with unresponsiveness to hypocapnia, loss of autoregulation, and reduced oxygen consumption of the arteriolar wall. Since immediately following head injury there was transient, marked elevation of the arterial blood pressure and since acute severe hypertension can produce the same changes in the pial microcirculation, we explored the possibility that this brief hypertensive episode might be responsible for the microcirculatory changes secondary to head injury. Anesthetized cats were subjected to severe (2-4 atm) fluid percussion head injury while the rise in arterial blood pressure was prevented by connecting the aorta to a reservoir set at a predetermined height and, if necessary, by the intravenous infusion of a vasodilator agent (ATP). Under these circumstances, head injury, which in experiments with uncontrolled blood pressure consistently leads to vasodilation, produced no significant change in vessel caliber. The vessels after such head injury remained normally responsive to hypocapnia. We conclude that the microcirculatory changes following experimental head injury are due to the associated acute elevation in blood pressure.

Neurophysiology of Transient Cerebral Ischemia in the Gerbil — Gaudet RJ, Welch KMA (Baylor College of Medicine, Houston, Texas)

The effect of transient unilateral common carotid artery (CCA) occlusion on electrocorticogram (ECoG), DC potentials and cerebral blood flow (CBF) was studied in 30 gerbils implanted with platinum electrodes. Brief ether anesthesia was used only during vessel occlusion to make behavioral observations possible. In 11 animals ECoG became isoelectric in the occluded hemisphere 46.3 ± 30.7 sec after occlusion and cortical depolarization followed within 3 to 4
minutes. Of these animals, 7 showed ECoG depression in the non-occluded hemisphere. Development of hemiparesis, seizures and circling was closely associated with ECoG depression. ECoG recovered from 30 minutes of occlusion after 30.8 ± 9.7 minutes of reflow. After occlusion for 60 minutes recovery was more variable. A negative DC shift often developed immediately upon reflow. Circling behavior and seizures recurred after reperfusion. CBF measured by \( H_2 \) washout 1 hour after reflow was lower (0.49 ± 0.22 ml/mg/min) in those animals with previous ECoG depression than in unaffected animals (0.76 ± 0.20 ml/mg/min). After CCA occlusion CBF fell to 0.02 and 0.34 ml/mg/min respectively. Relationships between CBF decrease, behavioral deficits, ECoG depression and DC shifts further substantiate the gerbil ischemic model. Recovery of neuroelectric activity after reflow depends on duration of ischemia.

IV-10

Alterations in the Cortical Oxygen Tension During the Development of Ischemic Cerebral Edema in Primates (M. mulatta) — Bremer AM, Yamada K, West CR (Roswell Park Memorial Institute, Buffalo, New York)

With a closed-head primate stroke model, acute MCA occlusion was produced by experimental embolism. Measurements in the PO\(_2\) at cerebral cortex-CSF interface were obtained by continuous on-line mass spectrometry. Determinations in % solids, tissue (Na) and (K) from the affected and opposite hemisphere at various times. With this preparation we registered the precise onset of cortical PO\(_2\) depletion, which showed an exponential downward trend (fast component from 0–5 min, \( t_m = 0.8 \) min, rate of change: 89% per min; slow component from 5–240 min, \( t_m = 258 \) min, rate of change: 0.3% per min). The reduced cortical PO\(_2\) observed at 1–2 h were similar, but these values were significantly different from the 3–4 h values (\( p < 0.025 \)). By this time, samples from the cortex supplied by the occluded MCA began to show excess in water, influx of (Na) and efflux of (K). The significant cortical PO\(_2\) reduction by 3–4 h of focal cerebral ischemia, was probably the result of a further reduction in O\(_2\) delivery to the ischemic cortex by the adverse effect of cerebral edema on collateral circulation. Our results agree with data derived from morphological studies suggesting that microvascular narrowing secondary to ischemic cerebral edema is significant by this time.

IV-11

A New Cerebral Blood Flow Technique. Xenon Enhanced CT Scanning — Drayer BP, Wolfson SK, Reinmuth OM, Du-jovny M, Boehnke M, Cook EE (University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania)

Xenon, a freely diffusible inert gas with atomic number 54, is readily visualized by CT scanning. Thus, brain enhancement, perfusion, and blood flow may be monitored.

An evaluation of cerebral blood flow was obtained in 5 adolescent baboons (Papio anubis/cynocephalus). Blood flow measurements were made with the arterial CO\(_2\) in a normal range as well as with decreased and increased CO\(_2\). On achieving a 70 to 80% concentration of Xenon by inhalation, a baseline CT scan was performed followed by 8 serial CT scans at 1.5 minute intervals during Xenon washout with oxygen. A clearance curve of Xenon was thus obtained by comparing the decreasing increases in the attenuation coefficient above baseline by visual and numerical techniques.

The normocapnic blood flow values using Xenon CT were consistent with those obtained in baboons by other investigators with traditional techniques. With hypercapnia, an increase in blood flow occurred while hypocapnia produced a marked diminution in cerebral blood flow. With further refinements in scanner technology, this technique should provide an important direct means of studying local cerebral blood flow.

SESSION V: SUBARACHNOID HEMORRHAGE; VASOSPASM

Friday (4:00-6:00 p.m.)

V-1

Structural Changes in Human Cerebral Arteries Following Subarachnoid Hemorrhage and Spasm — Peerless SJ, Hunter I, Drake CG (University Hospital, London, Canada)

Detailed histologic examination of large and small cerebral arteries using both light and electron microscopy was performed in 10 patients dying following subarachnoid hemorrhage. Each case had angiographic evidence of severe reactive vascular narrowing or spasm with secondary ischemic damage to brain. Four died within 3 weeks of the onset of the spasm syndrome and demonstrated mainly focal necrosis of the media in large conducting arteries typically at sites of maximum narrowing on the angiogram. The remaining 6 died 3–12 weeks following the demonstration of spasm and showed more widespread changes of medial necrosis, fibrosis and subendothelial thickening. All cases exhibited areas of focal narrowing of transcerebral arterioles and capillaries but without distinct changes in the wall. The pathogenesis and therapeutic implications of these observations will be discussed.

V-2

Ultrastructural Changes in Feline Arterial Endothelium Following Subarachnoid Hemorrhage — Mayberg MR, Houser OW, Sundt TM Jr (Mayo Clinic, Rochester, Minnesota)

Alteration of the endothelial surface and thrombogenesis in cerebral arteries associated with vasospasm following subarachnoid hemorrhage represents an attractive hypothesis for the pathogenesis of the secondary ischemic deficits. We have developed a model to assess the temporal course of ultrastructural changes in the feline basilar artery luminal surface following intracisternal injection of autogenous arterial blood. Serial angiography of the verteobasilar circulation in 5 control and 25 experimental animals at 4 hours and 1, 3, 5, and 7 days after subarachnoid hemorrhage was followed by in vivo perfusion fixation of the cerebral arteries. Scanning electron microscopy of basilar arterial endothelium showed longitudinal furrows which correlated with angiographically demonstrated vasospasm. These ridges were not present in control specimens, persisted with fixation at physiological pressure, and probably
reflected medial contraction with undulation of the underlying elastic lamina. No change in endothelial cell morphology or thrombogenesis was observed through 7 days following subarachnoid hemorrhage. There is no evidence from this study to suggest that ischemia related to vasospasm is a product of thromboembolism from damaged endothelial surfaces.

V-3

The Formation of Prostaglandins by Cerebral Arteries — Hagen AA, White RP, Terragno NA, Terragno A, Robertson JT (University of Tennessee Center for the Health Sciences, Memphis, Tennessee)

Prostaglandins E₂ and F₂α (PGE₂ and PGF₂α) and thromboxane A₂ (TXA₂) are all spasmodic when applied to cerebral vessels. Thus, they have been implicated as playing a role in the etiology of cerebral vasospasm following subarachnoid hemorrhage. Reportedly, the PG's are released from platelets. Whether the cerebral vessels might be capable of synthesizing PG's is not well established. Studies were initiated to investigate whether cerebral vessels did, indeed, have this capacity. Fresh porcine cerebral arteries were washed to remove residual blood and stripped of surrounding tissue. After slicing, the tissue was incubated in phosphate buffer, pH 8.0, and 2mM glutathione for 1 hour at 37°C. Following extraction and purification the samples were chromatographed on silica gel TLC. Evidence for both PGF₂α and PGE₂ was present. Bioassay by parallel superfusion of various tissues confirmed prostaglandin-like activity, approximately 200 ng/gm tissue. These results demonstrate that cerebral vessels can be a source of PG's and suggest this source may be important in the pathogenesis of cerebral vasospasm.

V-4

Microsurgical Anatomy of the Posterior Cerebral Artery (PCA) — Zeal AA, Rhoton AL (University of Florida, Gainesville, Florida)

The microsurgical relationships important in surgical approaches to the posterior cerebral artery and the neuroanatomic basis of syndromes related to thalamogeniculate and thalamoperforating arteries were defined in 50 cerebral hemispheres from cadavers. A new classification dividing approaches to the posterior cerebral artery and the neurovascular plexus were the medial and lateral posterior choroidal arteries; the former usually arose from P₂A and the latter arose as a series of arteries from P₂P.

V-5

Vessel Wall Response to End-to-Side Anastomosis — Mehdorn HM, Weinstein PR, Chater NL (University of California, San Francisco, California)

Microsurgical end-to-side anastomosis is used in extra- to intracranial arterial bypass (EIAAB) surgery for augmentation of collateral cerebral blood flow. To study the effects of such anastomosis upon both donor and recipient vessel walls, we used as a model end-to-side anastomosis between the rat femoral artery and vein. The anastomosis was performed under the operating microscope with eight 10-0 sutures. Vessels were removed after perfusion fixation in vivo and prepared for light and scanning microscopy 30 min to 6 weeks after surgery. All 30 anastomoses remained patent, the vessels usually forming an angle of 90 degrees. Endothelial regeneration occurs in the direction of blood flow. Fibrin deposition occurs on denuded subendothelial surfaces, followed by platelet adhesion and re-endothelialization. The time pattern of the healing is similar to that demonstrated for end-to-end anastomosis. The venous endothelium shows changes which suggest arterialization of the vein, such as roughening of the usually smooth surface and the appearance of folding. These SEM findings are confirmed by light microscopy. Both artery and vein are able to change their appearance according to an increase in flow and pressure, as demonstrated histologically.

V-6

Effect of Proximal Occlusion on Anastomosis Patency — Levinthal R, Moseley J, Stern WE (UCLA Medical Center, Los Angeles, California)

This study was conducted to compare superficial temporal-middle cerebral artery (STA-MCA) anastomosis patency in animals with and without proximal embolic MCA occlusion. Sixteen dogs underwent STA-MCA bypass in association with silicone embolization of the MCA via an internal carotid artery injection. The blood pressure and arterial blood gases were monitored and all procedures were performed by the same surgeon. Animals were re-explored 3–5 days postoperatively and anastomosis patency was evaluated by Evans blue injection and directly cutting of the STA. One hundred percent (10 of 10) of the dogs with proximal MCA emboli had a patent anastomosis whereas only 33-1/3% (2 of 6) without proximal MCA occlusion had a patent connection.

The likelihood of an anastomosis remaining open appears to be greatly influenced by the potential flow gradient between the extracranial and intracranial circulation.

V-7

Reversal of Ischemic Deficits by Induced Arterial Hypertension — Kassell NF, Peerless SJ, Drake CG (University of Iowa, Iowa City, Iowa)

Arterial hypertension was induced in an attempt to improve blood flow and reverse progressive neurological deficits from ischemia in 15 patients with thromboembolic
or iatrogenic stenoses or occlusion of cerebral arteries, or with vasospasm after subarachnoid hemorrhage.

In most instances dramatic temporary or permanent improvement in neurological function occurred. There were, however, disappointing failures and major complications, frequently related to inability to maintain arterial hypertension in the initial cases.

A technique for producing sustained arterial hypertension with vasopressor agents, intravascular hypervolemia and vagal blocking agents will be described.

V-8

Treatment of Subarachnoid Hemorrhage with Tranexamic Acid (A Double-Blind Clinical Trial) — Chandra B (University of Airlangga, School of Medicine, Surabaya, Indonesia)

Surabaya, the second largest city of Indonesia, has a population of 60 million and only one neurosurgeon. Subarachnoid hemorrhage is mostly treated medically. Our experience suggests that treatment with tranexamic acid should be recommended when surgery is not possible.

V-9

Major Reduction in Death from One Form of Stroke — Slosberg PS (The Mount Sinai Medical Center, New York, New York)

The effectiveness of medical-hypotensive therapy, already proven in the early phases of ruptured intracranial aneurysm, was evaluated in long-term follow-up (9 weeks and thereafter) of these same patients. The series comprises 106 patients with proven ruptured intracranial aneurysms who were treated medically with hypotension and followed up to 22 years. It includes far more difficult cases (many inoperable) than those reported in any surgical series. The method used had been introduced by the author in 1956 and improved subsequently. In the last 15 consecutive years, death from recurrent aneurysmal rupture in long-term follow-up has occurred in only one patient — and this latter is a presumed (unverified) hemorrhage. Thus far, 5 patients have been followed more than 20 years each; 4 patients have already passed the age of 80 years. Death from late recurrent aneurysmal hemorrhage has thus been markedly reduced by long-term medical-hypotensive therapy. In addition, no significant treatment morbidity has been found. These results, therefore, are better than those of any other known method of treatment, medical or microsurgical, reported anywhere to date.

V-10

Effects of Clinical Severity and Angiographic Findings on Long-Term Survivorship in Unilateral Cerebral Infarction Patients: A Prospective Study — Lee MC, Loewenson RB, Klassen AC, Resch JA, Gold LH (University of Minnesota, Minneapolis, Minnesota)

Effects of clinical severity and angiographic findings on long-term survivorship were evaluated in 91 survivors of initial unilateral cerebral infarction. Clinical severity was categorized into I mild (mild sensory or motor deficit), II moderate (sensory and motor deficits) and III severe (sensory and/or motor deficits with depressed sensorium). Angiographic findings of the involved side were divided into normal, <50% stenosis, ±50% stenosis and occlusion. In severity I (26 patients) the angiographic findings were: normal, 35% (9); <50% stenosis, 46% (12); ±50% stenosis, 8% (2); occlusion, 12% (3); in II (53): 15% (8); 47% (25); 6% (3), 32% (17); and in III (12): 17% (2); 33% (4); 17% (2); 33% (4).

Five-year survival rates were: clinical severity I, 68%; II, 58% and III, 31%. Five-year survival rates based on angiographic findings were: normal, 52%; stenosis (any degree), 50%; occlusion, 71%. Age was comparable among these groups with mean ages between 60 and 63. These results indicate that there is poor correlation between initial clinical severity and angiographic abnormalities. Long-term survivorship was lowest in patients with severe neurological deficit, but not related to angiographic findings.

V-11

Acute Experimental Subarachnoid Hemorrhage — Grady PA, Blaumanis OR, Nelson E (University of Maryland, Baltimore, Maryland)

Cardiovascular and respiratory dynamics and intracranial pressure (ICP) in experimental subarachnoid hemorrhage (SAH) were studied in dogs under light nitrous oxide anesthesia. SAH was created by slipping an externalized ligature from the cut end of a posterior communicating artery. The earliest detectable event following SAH was a marked elevation in ICP. The ICP typically rose to 75–90 mmHg within the first minute after onset of SAH, slowly declined over the next twenty minutes and thereafter remained elevated at about 40 mmHg. SAH was rapidly followed by transient bradycardia which subsided as blood pressure began to rise. Despite the typical pressor response cerebral perfusion pressure was decreased to levels as low as 45 mmHg. SAH was followed by marked alteration in respiratory patterns consisting of an initial increase in rate, a subsequent slowing and an increase in depth of respiration. The cardiovascular and respiratory response to acute SAH resembles, in many respects, the classic Cushing reflex. A sustained decrease in cerebral perfusion pressure and cyclic cardiovascular and respiratory instability in the first stage may be a factor in the deteriorating state which often follows subarachnoid hemorrhage.

V-12

Thalamic Hemorrhage and Arterial Blood Pressure Monitoring — McGraw CP, Barnes RW (Bowman Gray School of Medicine, Winston-Salem, North Carolina)
Arterial blood pressure monitoring can be misleading. Direct monitoring of cerebral perfusion pressure (MABP-ICP = CPP) has proved helpful in five thalamic hemorrhage patients as well as in other acute stroke patients. In these five patients, unreliability of indirect blood pressure monitoring and the need for direct arterial blood pressure monitoring was demonstrated. These patients had repeated minor episodes of muscle rigidity every 1 to 8 minutes. During these episodes, the blood pressure was often twice as high as when these episodes were not occurring. The stimulation of the nurse taking vital signs initiated these episodes and blood pressure readings being taken by the sphygmomanometer were consistently falsely high. With treatment on the basis of such a high blood pressure, cerebral perfusion pressure was reduced to damaging low levels (<60 mmHg) during the time when the episodes were not present. Continuous monitoring of direct arterial blood pressure allowed determination of such occurrences and, in three of these patients, these incidents ceased when diphenylhydantoin therapy was substituted for hypotensive therapy.

**SESSION VI: SURGICAL ASPECTS**

Saturday (8:00–10:00 a.m.)

**VI-1**

This study of 90 patients (58 arteries with angiographic evaluation) was performed to assess the accuracy of plethysmographic, ultrasonic methods and bruit analysis in detecting carotid disease. Arterial diameter narrowing >10% was considered positive for the purpose of comparison. (1) Oculoplethysmography. One false positive, false negatives in 2 patients with unilateral disease. In 6 of 15 patients with bilateral disease the test was negative. In 7 it was considered unilateral only. (2) Bruit Analysis was disappointing in predicting the location and extent of disease. (3) Supraorbital Doppler, positive in 14 sides but had a false negative rate of 60%. (4) Velocity Tracings from the neck arteries gave one false positive with false negatives occurring in 33% (13 of 40 sides). (5) Ultrasonic Arteriography. One false positive with false negatives in 8 sides, 14%. (6) Ultrasonic Duplex Scanning. One false positive with a 21% (10 of 48) false negative rate. With the ultrasonic methods (5) and (6) the majority of the errors (75%) were made with stenoses <50%. Real time spectral analysis of the velocity signals has been added to improve the detection of the earlier lesions.

**VI-2**
Comparative Study of Carotid Ultrasonic Arteriography and Oculoplethysmography with Contrast Angiography — Hajjar WM, Sumner DS (School of Medicine, Southern Illinois University, Springfield, Illinois)

Pulsed ultrasonic carotid arteriography and pulse-delay oculoplethysmography were carried out on patients with clinical symptoms of cerebrovascular insufficiency. Results were evaluated by contrast angiography.

Ultrasonic arteriography (U.A.) is done while patient is in the supine position. An ultrasonic probe with pulsed 5 MHz frequency is held by a position-sensing arm, which permitted sequential probe scanning over the carotid artery. To date, 76 vessels of 38 patients who have undergone oculoplethysmography (O.P.), have been scanned using this technique.

Twenty-four patients had positive studies using U.A. and 20 of those 24 patients had positive O.P. studies.

Ultrasonic arteriography was found to be 96% accurate (46/48 vessels) in determining the location and severity of extracranial arterial disease, when compared with x-ray findings, while oculoplethysmography method was found to be 82% (20/24 patients) accurate in detecting unilateral disease. Ultrasonic arteriography offered a simple but powerful clinical procedure for evaluation of extracranial circulation when compared with oculoplethysmography. Further studies are underway in our laboratory.

**VI-3**
Further Results on 2000 Carotid Bifurcations Examined with the White-Curry Arterial Colour Scan — White DN, Curry GR (Kingston General Hospital, Kingston, Ontario)

At the Second Joint Meeting in 1977 we described results obtained with the White-Curry Arterial Colour Scan in displaying occlusions and stenoses in the region of the carotid bifurcation.

Our experience now extends to the examination of 2000 carotid bifurcations in which the technique appeared to be remarkably accurate in displaying stenoses which close over 50% of the arterial lumen. Such localized stenoses must be distinguished from cases in which the velocity throughout an entire arterial segment is increased as the result of stenosis or occlusion of neighboring vessels in the ipsilateral or contralateral carotid bifurcation.

The display of occlusions is also accurate except in cases where stenosis proximal to the region scanned has abnormally slow flow through the carotid system below the threshold for display. Formerly occlusions might be falsely diagnosed as a result of an aberrant course in the vessels at 90 degrees to the beam and thus returning no Doppler shifted signals. This defect has been overcome by redesigning the scanning system.

**VI-4**
Noninvasive Imaging of Intracranial Arteries using 1 MHz Ultrasound — Barnes RW, Riley WA, McKinney WM, Toole JF, (Bowman Gray School of Medicine, Winston-Salem, North Carolina)

A 1 MHz linear phased array ultrasound system has been constructed to produce a two-dimensional image of intracranial anatomy and particularly the major intracranial arteries over about a 2 cm length. The major intracranial arteries detected include the internal carotids in the intradural part of the siphon, the middle cerebrials as they travel laterally from the internal carotids, the basilar artery, the posterior cerebrials as they follow the lateral aspect of the
Transient Ischemic Attacks Following Internal Carotid Occlusion — Barnes RW, Jarrell BE, Mendez-Picon G, Garrett WV (Medical College of Virginia, Richmond, Virginia)

Nine patients were evaluated for persistent amaurosis fugax (6), transient hemispheric ischemia (2) or both (1) following angiographic documentation of occlusion of the internal carotid artery. Eight patients had stenosis of the ipsilateral external carotid artery and 1 had common carotid artery occlusion. All had Doppler ultrasonic confirmation of reversed ophthalmic artery collateral flow via the ipsilateral temporal (6), infraorbital (1) or facial artery (1) or the contralateral facial artery (1).

The eight patients with external carotid artery stenosis underwent external carotid endarterectomy. All had relief of transient ischemic attacks for up to 3½ years. One patient developed recurrent amaurosis fugax at one year and was relieved following repeat endarterectomy for recurrent stenosis. The patient with common carotid occlusion became asymptomatic following subclavian-external carotid bypass. With Doppler confirmation of extracranial collateral circulation in a patient with internal carotid occlusion, persistent transient ischemic attacks may be effectively treated by external carotid reconstruction.

Improved Results of Carotid Endarterectomy in Patients with Symptomatic Coronary Disease — Ennix CR Jr, Lawrie GM, Morris GC Jr, Crawford ES, Howell JF (Baylor College of Medicine, Houston, Texas)

The significant risk of fatal myocardial infarction (MI) after carotid endarterectomy (CE) in patients with symptomatic coronary disease is well recognized. In 1290 consecutive patients undergoing carotid endarterectomy over the last 7 years, we have routinely determined the presence or absence of coexistent coronary disease. Although 41% (529/1290) of patients had a history of MI or electrocardiographic changes, only 21% (271/1290) had frank cardiac symptoms. The operative mortality in the 1019 patients without cardiac symptoms was 1.1% (11/1019). Of the 271 symptomatic patients, 152 underwent CE without prior coronary artery bypass operation (CAB) with an operative mortality of 17.1% (26/152). The other 119 patients were treated by either prior CAB or simultaneous CE and CAB with an operative mortality of 3.5% (4/119).

The greatly improved survival in those patients with cardiac symptoms who underwent CAB prior to or at the same time as CE and the absence of permanent neurological deficit in the 43 or these 119 patients who underwent simultaneous CE and CAB suggest that significantly improved survival can be achieved after CE in these high risk patients by the addition of simultaneous CAB.

Carotid Artery Lesions Causing Vertebral-Basilar Insufficiency — Correll JW, Stern J (Neurological Institute, New York, New York)

It has been reported that surgical reconstruction of a diseased carotid artery can relieve transient ischemic attacks in the vertebral-basilar distribution. In this report patients with symptoms of vertebral-basilar insufficiency treated by carotid endarterectomy are studied.

Two patients with anomalous branches from the internal carotid artery (one a persistent trigeminal artery and the other a persistent hypoglossal artery) supplying the basilar artery were completely relieved by carotid surgery. A number of other patients benefited from carotid surgery, but in some patients the vertebral-basilar symptoms persisted despite operation.

A review of this patient population is undertaken. It is felt that the following factors are of prognostic value in predicting which patients will benefit from carotid surgery: the type of carotid lesion, whether a source of emboli or of reduced blood flow, the patency of the circle of Willis, the collateral circulation and the adequacy of the vertebral arteries. These factors will be presented and discussed.

Changes of Topographical Regional Cerebral Blood Flow after Medical and Surgical Treatment of Stroke, Evaluated by 88Kr-Positron Emission Tomography — Yamamoto YL, Little J, Meyer E, Feindel W. (Montreal Neurological Institute, Montreal, Quebec)

Measurement of quantitative and topographical rCBF in every cm² of a cross section of the head is possible with a circular positron device using the non-invasive 88Kr inhalation technique. We have used this technique to evaluate topographical changes of rCBF in 64 patients with occlusive cerebrovascular disease, before and after medical and surgical treatment. Direct measurement of rCBF in the exposed brain was also performed using the 133Xe clearance technique with multichannel semiconductor detectors, before and after the anastomosis of the superficial temporal artery and middle cerebral artery in 6 patients. Our findings indicate that by 5% CO₂ inhalation, rCBF in cortical ischemic lesions is moderately improved, and rCBF in subcortical ischemic lesions does not improve significantly. However, following by-pass surgery, rCBF is not only markedly improved in both the cortical and subcortical ischemic lesions but the improvement is of a much higher magnitude than that achieved with 5% CO₂ inhalation.

Cortical Mitochondrial Respiration with Altered FiO₂ in Patients Undergoing Microanastomosis — Austin GA (Loma Linda University School of Medicine, Loma Linda, California)
In 26 patients undergoing microanastomosis for brain ischemia, intraoperative measurements of cortical metabolism were made. These included relative cortical PO_2 (bPO_2) made polarographically with a 25 µ teflon coated microelectrode, cortical electric activity (ECoG), and approximation of the cortical redox state of cytochrome a, a_3, and a_4. The STA-MCA anastomosis provided a means of altering local derangements of blood flow patterns. This is not possible with conventional cervico-thoracic operations for stroke which produce a diffuse augmentation of CBF.

VI-10

Reversal of Intracerebral Nutrient Steal Phenomenon after STA-MCA Bypass Graft — Fein JM (Albert Einstein College of Medicine, Bronx, New York)

The STA-MCA microanastomosis provides a means of altering local derangements of blood flow patterns. This is not possible with conventional cervico-thoracic operations for stroke which produce a diffuse augmentation of CBF.

Four patients in our series of bypass grafts showed preoperative evidence of intracerebral steal phenomenon which were reversed by STA-MCA anastomosis. This was documented with cineangiography and noninvasive regional cerebral blood flow studies. One patient had a stable dense right hemiparesis associated with bilateral middle cerebral artery stenosis. After a prophylactic right STA-MCA microanastomosis there was rapid resolution of the left hemisphere syndrome. Postoperative angiography and blood flow studies showed a redistribution of flow from right to left hemisphere to account for the clinical change. Two other patients with M1 occlusions showed ipsilateral intracerebral steal phenomenon from frontal to parietal regions in one and from occipital to frontotemporal region in the other. Neurologic deficits were related to areas from which blood flow was drawn. One patient with an internal carotid occlusion had a decreased visual acuity and a reversal of flow in the ophthalmic artery to augment middle cerebral flow. Normalization of flow in the ophthalmic artery bypass resulted in a three-fold increase in visual acuity. It is suggested that alteration of flow patterns rather than flow rate by microanastomosis may be responsible for resolution of cerebrovascular insufficiency caused both by intracerebral steal phenomena as well as microemboli.

VI-11

Long-Term Clinical Results of Superficial Temporal Artery-Middle Cerebral Artery Anastomoses (STA-MCA) in Stroke Patients — Ausman JI, Lee MC, Geiger J, Klassen AC, Chou SN (University of Minnesota, Minneapolis, Minnesota)

Results of STA-MCA anastomoses in anterior cerebral ischemia/infarction were analyzed in our first 40 patients (6 with TIAs, 26 with PRINDs, and 8 with moderate to severe infarctions). A neurologist observer (ML) recorded independently the patient's pre- and postoperative medical and neurological history and objective neurological findings. Mean age was 55 years (range 29-71). Average time between onset of stroke and surgical procedure was 6 months (range 1-48 mo), while the duration of follow up studies was 14 mo (range 3-37 mo). Angiography revealed 32 internal carotid occlusions (23 unilateral, 9 bilateral), 3 carotid siphon or middle cerebral artery occlusions or stenosis and 5 multiple extra and intracranial occlusions.

There was no operative mortality. Four patients expired from probable myocardial infarctions. During the followup period, no patient suffered recurrent cerebral infarctions; 2 patients experienced a single TIA; 2 others had recurrent amaurosis fugax. Neurological deficits were either unchanged (21 patients) or improved (19 patients).

The results strongly suggest that this procedure may reduce stroke recurrence and also result in improvement of neurologic dysfunction in these revascularized patients.

SESSION VII: CLINICAL ASPECTS

Saturday (10:30-12:30 p.m.)

VII-1

Natural History of Anterior Spinal Artery Thrombosis — Satran R (University of Rochester School of Medicine, Rochester, New York)

The presentation and course of 8 patients diagnosed as having spinal cord infarction secondary to anterior spinal artery occlusion were reviewed. Abrupt onset of abdominal pain and backache of varying severity plus lower limb weakness signaled the onset of illness in 7 of this group. Tetraparesis occurred in one patient who sustained a concomitant myocardial infarction. In 2 patients motor deficits evolved over a period of hours. Flaccidity of the lower limbs was the most common motor finding. All had impaired bladder function save one whose physical findings indicated occlusion of a sulcal artery. More than half the patients had peripheral vascular disease or hypertension.

Despite profound weakness early in the course of illness prognosis for recovery of function appears favorable. Seven of the patients who had serial examinations improved to the point of being able to ambulate either independently or with minor assistance.

VII-2

Fibromuscular Dysplasia of Cerebral Arteries: An Important Cause of Recurrent Strokes and Moya Moya Syndrome — Merkel KHH (University of Miami, Miami, Florida)

Recently two young patients presented at our hospital with symptoms of recurrent strokes over a one-year period...
THIRD JOINT MEETING ON STROKE AND CEREBRAL CIRCULATION

unti they died. Shortly before death bilateral carotid arteriograms showed radiographical occlusion of large intracerebral arteries and the distinct picture of the moyamoya syndrome. Autopsies revealed 2 processes responsible for occlusion of the distal segment of the internal carotid arteries and posterior communicating arteries. They were 1) exuberant intimal hyperplasia with and without medial fibrosis and hypoplasia (fibromuscular dysplasia) and 2) old and recent thrombi. The arteries in other organs were not involved by this process. These findings and the review of autopsy reports of the moyamoya syndrome indicate the prime importance of fibromuscular dysplasia in the development of this syndrome.

VII-3

Temporal Profile of Acute Vertebrobasilar System Infarction — Jones HR, Millikan CH, Sandok BA (Leahy Clinic, Boston, Massachusetts)

The records of 220 consecutive patients with acute cerebral infarction seen at a Mayo Clinic affiliated hospital within 36 hours were retrospectively reviewed. 179 patients had carotid system infarction (CSI), four were unclassified as to system and the remaining 37 patients had VBI.

The temporal profile of each patient was categorized from the onset during the first week as: 4 normal, 16 improved, 7 no improvement, 10 dead.

The mortality of 27.5% for VBI is 2.7 times greater than that seen with CSI (10.6%) and was confined to the group showing progressive systematology. In this uncontrolled study, the anticoagulant therapy (A/C rx) administered to half the patients with progressive VBI was associated with a 33% mortality. The remaining patients in this group received no A/C rx and displayed a similar mortality. We are unable to draw conclusions as to value of the A/C rx since the patient groups were not similar.

In view of the therapeutic approaches now being suggested for the management of VBI, these data may provide a baseline for further evaluation.

VII-4

Regional Cerebral Dysautoregulation in Pathogenesis of TIAs within the Vertebro-Basilar Arterial System — Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Pollack P (Baylor College of Medicine, Houston, Texas)

36 patients with vertebrobasilar insufficiency (VBI) were investigated by 133Xe inhalation measurements of rCBF. Mean age was 59 ± 10 years. In 27 patients autoregulation was tested by decreasing blood pressure by postural tilting. Autoregulation was also tested in 15 normal volunteers (mean 53 ± 10) for comparison.

When measured lying flat, mean hemispheric and brainstem-cerebellar values for F, were not significantly different from age-matched normal controls, although MABP was significantly increased in VBI patients. Mean arterial blood pressure was reduced by about 11 mm Hg in VBI and normals by postural tilting. Mean hemispheric and brainstem-cerebellar F, values were significantly reduced in VBI patients but not in normals. Regional dysautoregulation was greater in severity in patients with symptoms present for 1 year or longer. TIAs in patients with VBI appear to be related more to dysautoregulation than to cerebral embolization.

VII-5

Age-Related Changes in Platelet Aggregability — Couch JR, Hassanein RS (University of Kansas, Kansas City, Kansas)

A study of age-related changes in platelet aggregation (PA) was carried out in 179 control subjects aged 10-80 to provide a baseline for comparison of PA in patients with stroke. PA was measured with optical-density techniques and a scoring system formulated based on the threshold of occurrence of phase II PA as follows: occurrence of phase II at 0.85 µM ADP was scored 70, at 1.275 scored 60, at 1.7 scored 50, at 2.55 scored 30 and at 3.7 µM ADP scored 10. Score adjustment between these intervals was based on percent disaggregation 3 minutes after peak PA (Th score). There were 10-30 subjects in each decade. For all 179 subjects the distribution of Th scores fit a bimodal normal distribution (p < .01) with means ± SD of 26.4 ± 10.6 for the lower and 58.2 ± 7.1 for the upper one. The lower distribution was termed normally aggregable (NA) and the upper one hyperaggregable (HA). Comparing by decades there was no difference in the HA/NA ratio from age 10-50, with 30% of subjects in the HA group. Beyond age 60, 80% of subjects were in the HA group. The difference in HA/NA distributions between subjects 10-50 years and 60+ years was highly significant (p < .001). This work shows there is a marked increase in PA which begins at age 50 and levels off at age 60. This increase in PA with age parallels and may contribute to the rising incidence of stroke with age.

VII-6

Sulfinpyrazone and Aspirin Therapy Compared on Platelet Function in Completed Stroke and Vertebro Basilar Insufficiency — Kite LD, Meyer JS, Gedye JL (Baylor College of Medicine, Houston, Texas)

Effects of sulfinpyrazone versus aspirin therapy on increased platelet adhesiveness and circulating microemboli (circulating microemboli index) were compared before and after therapy in three age- and sex-matched groups of 12 patients with vertebrobasilar insufficiency (VBI) and two matched groups of 16 patients with completed stroke. Comparable groups of VBI and stroke patients received 1200 mg aspirin daily, or 800 mg sulfinpyrazone daily. Another group of 12 VBI patients received sulfinpyrazone therapy first followed by aspirin therapy.

Platelet adhesiveness was reduced in both stroke (p < .0025) and VBI (p < .001) by each drug. Aspirin reduced circulating microemboli in both stroke (p < .001) and VBI (p < .001). Sulfinpyrazone reduced circulating microemboli in stroke patients (p < .0025) but not in VBI patients. When patients with VBI were changed from sulfinpyrazone to aspirin therapy platelet adhesiveness (p < .01) and circulating microemboli (p < .025) were significantly reduced. Aspirin is more effective in treatment of platelet dysfunction in stroke and VBI.
The rationale involves maintaining the viability of suboptimally functioning cells due to ischemia by hypersaturation of atmospheric pressures has been utilized in treatments of both acute and chronic stroke syndromes. A series of 3 cases of severe neurological deficit subsequent to embolic phenomena to the cerebrum were treated with hyperbaric oxygenation and good to excellent results were obtained. The rationale involves maintaining the viability of suboptimally functioning cells due to ischemia by hypersaturation with oxygen. Improvement in the EEG of patients with both acute and chronic stroke being treated with the modality have been recorded. Clinical improvement in these patients with improved EEG occurs. No untoward effects have resulted.

Hyperbaric oxygenation appears to be a valid mechanism in the treatment of specific stroke patients in both the acute and chronic stages. In addition to clinical observation, the EEG affords a method to determine the justification for utilization of hyperbaric oxygen treatments. It may also permit choosing those patients who are candidates for prompt surgical intervention in acute stroke.

Effects of \( \gamma \)-Hydroxybutyrate and \( \gamma \)-Butyrolactone upon the Energy Metabolism of the Hypoxic Brain — MacMillan VH (Department of Medicine, University of Toronto, Toronto, Ontario)

The beneficial effects of CNS depressants such as barbiturates on the metabolism of the hypoxic brain is well known. In order to assess the effects of the naturally occurring CNS depressant \( \gamma \)-hydroxybutyrate (GHB) and its lactone \( \gamma \)-butyrolactone (GBL) on the energy metabolism of the hypoxic brain, rats were given GHB (500mg/kg) or GBL (300 mg/kg) i.v. followed by 30 min exposure to \( \text{P}_{2\text{O}} \text{O}_2 \)'s of 25-30 mm Hg. GHB and GBL reduced the depletion of phosphocreatine (80% and 86% of control respectively) in comparison to hypoxemic controls (56% of control) and prevented the small decreases of adenosine triphosphate and increases of adenosine diphosphate observed at this level of hypoxemia. A major effect on the accumulation of lactate was observed with hypoxemic control values being 21.1; GHB and hypoxemia — 14.4; and GBL and hypoxemia —9.1 mM/kg i.e. \( \text{H}_2\text{O} \) respectively. In addition, animals receiving GHB or GBL showed larger increases of cerebral glucose (5.7 and 6.6 mM/kg respectively) in comparison to hypoxemic controls (3.7 mM/kg). The results indicate that GHB and GBL have a beneficial effect on the energy metabolism of the hypoxic brain and suggest their possible use in the management of the acutely hypoxic-oligemic brain.

Selection of High Response Groups in Cerebral Ischemia — Gent M (Faculty of Health Sciences, McMaster University, Hamilton, Ontario)

Because of the large number of patients required for valid inferences, studies of antithrombotic therapy in patients with transient cerebral ischemia are expensive, and compliance with the protocol is very demanding on both investigators and patients. In an attempt to reduce sample size requirements we often seek to identify "high risk" groups, e.g., history of multiple rather than single attacks, associated comorbidity, etc. However, this approach may sometimes be fallacious, indeed there is evidence to show this, and what is required is the identification of "high response" groups. Data from recent and current studies in cerebral and myocardial ischemia will be presented to show that some "high risk" groups are consistently unresponsive to therapy. On the other hand, relatively "low risk" groups are sometimes highly responsive. Procedures for identifying "high response" groups will be presented and the implications for future research design and publications discussed.

Canadian Cooperative Platelet-Inhibiting Drug Trial in Threatened Stroke — Barnett HJM (University Hospital, London, Ontario)

585 patients with transient or minor cerebral ischemic events were randomly allocated to a trial of aspirin, sulfinpyrazone, both or placebo and followed from the time of first entry into the study beginning in January, 1972 until June, 1977. The average duration of follow up was 1003 days. A followup of 99.3% was achieved and an analysis of the overall effectiveness of these platelet-suppressive agents indicates that the risk of continuing TIA, stroke or death is lowered in a statistically significant fashion in the aspirintreated but not the sulfinpyrazone-treated patient. Aspirin reduced the "harder" end-points of stroke and death by ap-
proximately one-third, with statistical significance ($p = 0.05$).

The favorable result related most particularly to the patients with more than single attacks, to the older patients, was largely confined to males, and was significant only when patients were not hypertensive at the time of entry into the study.

In the most favorable sub-group of normotensive males, a significant reduction ($p = 0.01$) of stroke and death approaching 50% during the period of follow-up was achieved by aspirin therapy.

Adjournment
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