SPECIAL ARTICLE

Summary of the Eighth Princeton Conference on Cerebral Vascular Diseases, January 5-7, 1972, Nassau Tavern, Princeton, New Jersey

PREPARED BY DR. C. H. MILLIKAN, EDITOR OF "STROKE—A JOURNAL OF CEREBRAL CIRCULATION"

The Conference opened on Wednesday, January 5, 1972, with a presentation by Dr. F. William Blaisdell, Professor of Surgery, University of California, San Francisco, California, entitled “Extracranial Arterial Surgery in the Treatment of Stroke.” Dr. Blaisdell presented data from a Joint Study of Extradural Cerebral Vascular Disease and chose to compare the survival in patients who had operative removal of arteriosclerotic lesions in extracranial arteries with the survival in patients treated in identical fashion medically, but who did not have surgery, as the focus of his presentation. There were 1,378 patients selected randomly for medical or surgical therapy; 693 patients had surgery and 685 had the “best medical treatment available.” Review of the randomized series as a whole shows that when the medical and surgical groups are compared: (1) there is no significant difference in survival, (2) patients with high blood pressure and evidence of heart disease had a significantly greater survival rate if they were managed medically, (3) there was no significant difference in mortality between the medically-managed and surgically-managed...
groups with unilateral carotid stenosis, although the survival in the surgical group was slightly higher at almost all follow-up intervals, (4) in patients with bilateral carotid stenosis a marked difference in survival in favor of the surgical group was noted, and (5) no improved survival was detected in patients with stenosis plus occlusion of the opposite carotid artery, although the medically managed group fared better than the group managed surgically.

Out of his own extensive experience, Dr. Blaisdell went on to emphasize that: (1) When arteriography shows a carotid plaque with irregularities suggesting ulceration, surgical treatment will probably be of benefit if symptoms can be related to neurological changes in the territory of the brain supplied by the artery. (2) Patients with disease of the carotid bifurcation seem to fare better when managed surgically than medically if the disability is mild and hypertension is present. (3) Angiography is indicated when the diagnosis of cerebral vascular disease is questionable and definitive diagnosis is needed. (4) The optimal patient for evaluation is the one who is having recurrent transient ischemic attacks in the distribution of a carotid artery. This group has a high incidence of subsequent stroke and also will usually be found to have an ulcerated atheroma at the carotid bifurcation. (5) Angiographical evaluation is not considered indicated in patients with an acute neurological deficit, in patients with a severe disability from a previous stroke, or in patients with heart disease. (6) Patients should not be operated upon within two weeks of the development of an acute neurological deficit with major residual. (7) Patients with a severe disability following a stroke will not be benefited by surgery and can be considered to have end-stage disease. Surgery offers hope of preventing additional strokes or deaths from strokes but it cannot reverse existing neurological deficits. (8) Patients with heart disease, particularly those with a history of findings compatible with myocardial infarction within six months of the proposed surgery or a disability from angina pectoris, have a short life expectancy and the risk of surgery is high. (9) If the symptoms strongly suggest recurrent cerebral emboli and the primary lesion, visualized on the angiograms, lies at the carotid bifurcation, then surgery is indicated and an ulcerated atheroma usually will be found.

Dr. William S. Fields, Houston, Texas, opened the discussion and reviewed the focal points and conclusions presented by Dr. Blaisdell. In addition, Dr. Fields mentioned that operation on asymptomatic carotid bruits is not justified.

In continuing discussion, Dr. Lewis H. Kuller, Associate Professor, School of Hygiene and Public Health, Johns Hopkins University of Baltimore, Maryland, presented a number of tables for discussion of the Joint Study of Extracranial Arterial Occlusion. He presented a number of factors that may have affected the results of the extracranial study as follows:

(1) Host
   (a) Patient selection
   (b) Prevalent versus incident cases
   (c) To extensive disease, past the critical point

(2) Environment
   (a) Diffuse atherosclerotic disease
   (b) Competing risk factors
   (c) Intracranial versus extracranial disease
   (d) Competing causes of death

(3) Agent (surgical therapy)
   (a) High initial surgical mortality
   (longer follow-up needed)
   (b) Inter-institution variation
   (c) Heterogeneous causes of disease

Dr. Kuller concluded that surgical treatment and medical treatment appear to be about equally effective as demonstrated by the Joint Study of Extracranial Arterial Occlusion.

Dr. C. H. Millikan, Professor of Neurology, Mayo Medical School, Rochester, Minnesota, concluded the formal discussion by initially commenting that collaborative studies: (1) were extraordinarily expensive, (2) sometimes were successful in getting new people into a particular field of interest, (3) provide a communications mechanism among workers interested in a particular disease, (4) should be undertaken only if there is no other way in getting an answer to a given question, and (5) sometimes provide some useful or even important bits of information—however, this outcome is dependent on whether the study is of simple design, concerns an easily defined problem with a precisely defined question, and is of limited time duration. He went on to say...
that it is now apparent that occlusive cerebral vascular disease includes such a complex set of symptoms, physical signs, and laboratory events—all occurring in a framework of changing severity (the temporal profile) and, in turn, importantly interrelated to profound systemic disorders including hypertension, heart disease, diabetes, and so forth—that the answers to key clinical questions have not and will not be forthcoming from the material put together by the Joint Study of Extracranial Cerebral Vascular Disease. Dr. Millikan enumerated specific criticisms, each of which would invalidate the results of the Joint Study. These included:

(1) No standard method for the treatment of the medically managed half of the patients who were supposed to be randomized! No one can tell whether the patients in this group, or how many of them, received anti-coagulants, had adequate treatment for hypertension, had cardiac arrhythmias controlled, had cardiac failure therapeutically solved, etc. This means that there is really no valid comparison group available.

(2) No mention is made of presence or absence of carotid or cranial bruits—a highly important clinical observation that in certain instances may be the deciding factor concerning a method of investigation of a given patient.

(3) No recording of presence or absence of retinal ischemia or of decrease, increase or normalcy of the retinal arterial blood pressure as measured by ophthalmodynamometry!

(4) Amazingly, the presence or absence of retinal emboli is not mentioned or apparently not recorded in the study. It was pointed out that the recurrence of transient ischemic attacks with the detection of embolization during a period of hours of observation by the examining physician may constitute an emergency indication for surgery on the carotid artery—this point, of course, is not even apparently recognized by the Joint Study.

(5) The unique nature of the transient ischemic attacks suffered by the patients reported in the Journal of the American Medical Association, March 23, 1970, where of 92 cases having (by four-vessel angiography) unilateral carotid stenosis only 32% had carotid transient ischemic attacks, while 47% had vertebral basilar transient ischemic attacks! According to Dr. Millikan no similar series of patients has ever been reported in the world's literature, and this amazing observation suggests that: (1) inaccurate histories were obtained in the first place, (2) data were incorrectly recorded and entered into the computer, (3) the angiograms either were of poor quality or were incorrectly interpreted, or (4) computer instructions and print-out were incorrect. Finally, Dr. Millikan emphasized that it was impossible to make any judgments concerning Dr. Blaisdell's report about the 1,378 randomized patients, not only because of the previously mentioned defects in the study, but because absolutely no data were included concerning the clinical state of these 1,378 patients. No information was provided as to how many had only transient ischemic attacks, how many had progressing stroke, how many had completed stroke or how many had completed stroke with subsequent transient ischemic attacks.

During subsequent lively discussion by Drs. Blaisdell, Fields, Hass and others, no new information was supplied to obviate the criticisms of the Joint Study.

The program for Thursday, January 6, 1972, opened with a report of the randomized treatment study (table 1) of the "Cooperative Aneurysm Project" by Dr. A. L. Sahs, Professor of Neurology, University of Iowa, and Dr. D. W. Nibbelink, Assistant Professor of Neurology, University of Iowa, Iowa City, Iowa. It was reported that the therapeutic objective of the drug-induced hypotensive treatment was to lower the blood pressure 20% when the systolic pressure was 140 or below, to lower the blood pressure 25% when the systolic pressure was 140 to 180, and to lower the blood pressure 30% when the systolic pressure was over 180 mm Hg. The drugs used

<table>
<thead>
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<th>Type of Treatment and Mortality of 959 Randomized Patients</th>
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<tr>
<td><strong>Type of treatment</strong></td>
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<tr>
<td>Regulated bed rest</td>
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<tr>
<td>Drug-induced hypotension</td>
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<tr>
<td>Carotid ligation</td>
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<td>Intracranial surgery</td>
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were chlorothiazide, reserpine, hydralazine, and methyldopa. The category referred to as "intracranial surgery" included a variety of procedures plus medications thought to combat cerebral edema. A variety of statistical methods were used in an attempt to compare the various methods of treatment depending upon the type of aneurysm, the condition of the patient and the number of days or years of follow-up.

The results of these analyses were that regulated bedrest was the poorest treatment, while drug-induced hypotension was the best treatment with common carotid ligation a close second best and particularly successful in the therapy of internal carotid artery aneurysms. However, the opinion of several discussers was so critical of the "Cooperative Aneurysm Project" design, data analysis and conclusions that the actual conclusions presented were certainly left unsubstantiated at the conclusion of the session.

Formal discussion was started by Dr. Bronson S. Ray, Professor of Surgery (Neurosurgery), Cornell University Medical College, New York, New York. He mentioned that he much prefers to individualize the study and treatment of each patient with subarachnoid hemorrhage, pays close attention to the control of discomfort as well as bowel and bladder function, uses steroids and osmotic agents to combat cerebral edema and may resort to frequent cerebral spinal fluid drainage to ease the patient's discomfort and decrease increased intracranial pressure.

Dr. Joseph Ransohoff, Professor of Neurosurgery, New York University College of Medicine, New York, New York, continued the discussion by vigorously criticizing the construction of the treatment groups under study. He mentioned that intracranial surgery is specifically designed to prevent further (long-term) bleeding, while regulated bedrest and drug-induced hypotension are entirely different items designed to prevent immediate re-bleeding. He went on to say that carotid ligation has been discontinued in his department and that immediate re-bleeding of patients with acute subarachnoid hemorrhage secondary to ruptured intracranial aneurysms has been held to an 8% level in 60 consecutive patients by the use of regulative hypotension and epsilon-aminocaproic acid (Amicar). Dr. Ransohoff concluded by repeating that the results of the randomized treatment study are "not valid" and of "historical interest only!"

Dr. Maureen Henderson, Professor of Preventive Medicine, University of Maryland School of Medicine, Baltimore, Maryland, concluded the formal discussion by presenting a fairly critical analysis of the statistical methods used—coming to the conclusion that no significant suggestions could be made concerning the treatment of ruptured intracranial aneurysm, from the data analysis presented.

During additional discussion, Dr. Alan Richardson, Department of Neurosurgery, Atkinson Morley's Hospital, London, England, reminded the attendees of the Conference that his own group had already pointed out by 1964 that internal carotid artery ligation was probably most effective for internal carotid artery aneurysm and that there was no really effective therapy for anterior cerebral-anterior communicating artery aneurysms, while surgery is certainly not indicated in the early phases of rupture of essentially any intracranial aneurysm!

Dr. Ellsworth C. Alvord, Professor of Pathology (Neuropathology), University of Washington, Seattle, Washington, presented an interesting table which he affirmed represented a straightforward way of predicting, on a percentile basis, the prognosis of a patient with subarachnoid hemorrhage, depending upon the patient's condition and the number of days elapsed after the rupture of the intracranial aneurysm (table 2).

Dr. James Toole, Professor of Neurology, Bowman Gray School of Medicine, Winston-Salem, North Carolina, described and showed a picture of an automatic tilt-table for the precise control of blood pressure. The patient is premedicated with antihypertensive drugs, the blood pressure is automatically recorded via an intra-arterial catheter, and the height of the blood pressure then, after computerized control, stimulates the tilt-table motor to make an appropriate re-adjustment of the tilt-table or tilt-bed.

In conclusion, Dr. Nibbelink, in response to a question, told the Conference that there was no difference in death rates between those patients with no known intracranial arterial spasm and localized arterial spasm! He added that there is some uncertainty about the impact...
Table 2

Probability of Survival for Two Years After Ruptured Intracranial Aneurysm

<table>
<thead>
<tr>
<th>Condition of patient</th>
<th>Days after rupture</th>
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<tr>
<td></td>
<td>0-1</td>
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<tr>
<td>Symptom free</td>
<td>65</td>
</tr>
<tr>
<td>Minimally ill, headache, stiff neck</td>
<td>55</td>
</tr>
<tr>
<td>Moderately ill, (a) lethargic with headache but no focal deficit or (b) alert with hemispheric deficit</td>
<td>45</td>
</tr>
<tr>
<td>Stuporous, (a) severely obtunded without major neurological deficit or (b) lethargic with neurological deficit</td>
<td>30</td>
</tr>
<tr>
<td>Moribund</td>
<td>5</td>
</tr>
</tbody>
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Add 5% for each probability—if survival for two months is desired.

of "severe diffuse arterial spasm" on mortality rates.

The next major topic introduced was cerebral ischemia, and there were nine presentations with numerous formal and informal discussions which occupied the remainder of Thursday, January 6, 1972, and continued during a portion of the morning session on Friday, January 7, 1972. The first major presentation was by Dr. J. B. Brierley, Medical Research Council Neuropsychiatric Unit, Medical Research Council Laboratories, Carshalton, Surrey, England, who described some of his observations of experimental cerebral ischemia. He mentioned the significant distinctions between circulatory arrest, overall reduction of flow and hypoxemia. Dr. Brierley raised the important question concerning when the initial changes of ischemia are still reversible. He suspects that mitochondria begin to become disorganized in 10 to 15 minutes of anoxemia and that this may represent the first irreversible change; however, some such cells seem to have normal organelles and it may be possible for these cells to return to function. Mention was made of the boundary zone locus of trouble in decompression experiments. It was pointed out that during the last half of 13 or 14 minutes of decompression there are bradycardia and hypotension as well as simple reduction of oxygen tension.

Dr. Robert Crowell of the Massachusetts General Hospital, Boston, Massachusetts, described experiments (monkeys) where a brain blood vessel was clipped and the installation of carbon black was used to demonstrate the patterns of altered blood supply at different points in time after the clipping of the artery. Dr. Crowell called attention to the considerable variability in the collateral patterns and that the abnormalities of filling were much more severe when associated with induced hypotension. The poor filling of vessels was limited to the areas of infarction—the exact mechanism was not known but Dr. Crowell wondered whether endothelial swelling might be an important factor.

Dr. Crowell went on to describe vascular permeability experiments in which Evans blue was injected at variable times after an intracranial artery was clipped. Up to three days following clipping no extravasation of Evans blue was noted; from three to 14 days following clipping there was frequent staining with the Evans blue, while after 28 days no staining was noticed.

In discussion Dr. Erland R. Nelson, Professor of Neurology, University of Maryland, Baltimore, Maryland, described observations he has made on the effects of ischemia on the endothelium of arteries of monkeys. Actual holes in the endothelial surfaces of the ischemic carotid arteries were beautifully clear in pictures presented by Dr. Nelson.

Dr. Adelbert Ames, III, Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts, continued the discussion by telling about the changes (cessation of respiration and marked hypotension) which occur when there is total cerebral ischemia. He emphasized that we do not know the first changes which are produced by ischemia in the very first seconds of an ischemic event. The cells swell from ischemia
alone, and the swelling of cells may decrease lumen size, and the flow of fluid out of the vascular bed into the extracellular spaces may increase the viscosity of the fluid in the vascular bed. Dr. Ames added that there is a distinction between a trickle of flow and no flow at all—that the physical distance of cells from the former may determine whether metabolic opportunities are adequate for cell life. The distinction between no flow and a decrease in oxygen availability has been demonstrated by experiments using the optic nerve in which certain interesting interrelationships were noted: oxygen absence being bad for function but not necessarily for survival, absence of glucose bad for recovery but not for immediate function, and absence of glucose and oxygen simultaneously being better for ultimate cell recovery than an absence of glucose alone.

A major presentation, "Cerebral Metabolism and Cerebral Ischemia," was made by Dr. Bo K. Siesjo of the Research Department, University Hospital, Lund, Sweden. He described the known concepts of energy utilization including a review of the assumed tissue (cellular) requirements. His experimental work suggests that lactic acidosis (related to cerebral ischemia) may be due to an outside stimulus and certainly is not due to a change in energy state.

Dr. Fred Plum, Professor of Neurology, Cornell University Medical College, New York, New York, opened the discussion with the observation that "perfusion is the critical issue to the maintenance of cell life." He went on to describe experiments in which perfusion pressure was kept normal; the experimental animals were not permitted to become acidotic while oxygen tension was lowered very significantly without producing significant infarction. The conclusion was that total perfusion is the important issue in preventing infarction and that the decrease in availability of oxygen does not appear to be the determining factor in the production of infarction.

"The Pathophysiology of Cerebral Ischemia" was the topic of the presentation by Dr. A. G. Waltz, Professor of Neurology, University of Minnesota School of Medicine, Minneapolis, Minnesota, who pointed out that ischemia is different than anoxia, that it is not realistic for one to consider the no-reflow phenomena in work with patients and that there are several paradoxical reactions to vasodilators, including occasional increases in intracranial pressure with the administration of carbon dioxide because of vasodilatation of vessels in normal areas of brain and the observation that hypercarbia seldom produces a decrease in cerebral blood flow. Dr. Waltz said that some patients will benefit from carbon dioxide inhalation, although no evidence from clinical experience was presented to confirm this.

Dr. O. M. Reinmuth, Professor of Neurology, University of Miami, Miami, Florida, opened the discussion by observing that he knew of no evidence which suggested any beneficial or detrimental effect on stroke patients from hypercapnia or hypocapnia! Dr. Reinmuth raised the interesting question as to whether an elevation of blood pressure, somewhat above the usual level of hypertension for an individual patient, might have some pathogenetic impact on the production of focal cerebral ischemia. In the disorder known as hypertensive encephalopathy there are often focal neurological abnormalities which suggest that there has been more effect of the pathophysiological process on one specific area of brain than on other areas of brain. Informal comment tended to be skeptical of the idea but the hypothesis bears further inspection.

Dr. Julio H. Garcia, Division of Neuropathology, University of Maryland, Baltimore, Maryland, discussed his observations concerning "The Reversibility of Cerebral Ischemia." He drew attention to the effects of short-duration ischemia on the kidney and showed examples of electron microscopic changes. Dr. Garcia told about observations concerning focal cerebral ischemia produced by occluding the middle cerebral artery through the orbit of an experimental animal. First changes appear to be multiple small foci of necrosis in an area which will be an infarct followed by the early structural abnormality which involves postsynaptic processes (early edema), after which there are early mitochondrial changes.

Dr. Frank M. Yatsu, Assistant Professor of Neurology, University of California, San Francisco, California, opened the discussion of Dr. Garcia's paper and listed the neurochemical changes, in sequence, which appear to lead up to the irreversibility of the changes associated with ischemia. In describing four such stages, Dr. Yatsu placed inadequate
glucose and oxygen supply along with the accumulation of the metabolites (lactic acid) in stage 1; reduced energy production and acidosis in stage 2; decreased AP'Tase, decreased ion gradient, decreased membrane potential, decreased synthesis of transmitters, decreased synthesis of cellular constituents (proteins—lipids), and activated catabolism (?) in the third stage; and no functional recovery in stage 4.

Dr. Jerome B. Posner, Professor of Neurology, Cornell University Medical College, New York, New York, summarized the advantages and disadvantages of the various methods for the study of cerebral blood flow. For instance (Dr. Posner did this for the various methods), he mentioned that the advantages of the O_15-labeled H_2O method included the ability to study regional blood flow and metabolism and to arrive at partition coefficients, and that there was little tissue absorption of the isotope. The disadvantages included problems of recirculation of the isotope, the short half-life of two minutes (which means that a cyclotron must be available), problems relating to collimation, and the need for carotid puncture. Dr. Posner concluded his careful analysis by discussing the clinical value of cerebral blood flow studies as they exist today and may be developed in the future. He listed: (1) carotid artery ligation, (2) diagnosis of cerebral ischemia, (3) carotid endarterectomy, (4) prognosis in coma and cerebral death, (5) treatment of stroke in brain injury, and (6) migraine as possible situations in which cerebral blood flow studies might be of value. Dr. Posner, however, then discussed each of these areas and was careful to point out that simpler and better methods, in each instance, already exist, and the clinical applicability of cerebral blood flow studies continues to be close to nonexistent.

Dr. O. M. Reinmuth realistically reminded the Conference attendees that methods of study which require bilateral or unilateral carotid puncture, or bilateral or unilateral jugular bulb or lateral sinus sampling, probably are contraindicated in the actual bedside management of moderately or acutely ill stroke patients. He mentioned that the precision of regional cerebral blood flow studies continues to be of questionable accuracy.

Dr. Olaf B. Paulson of the Bispebjerg Hospital, Copenhagen, Denmark, reported that clinical trials of the hyperventilation treatment of acute stroke have now demonstrated that this treatment is of no significant value. He discussed the limitation of blood flow methods relying on collimation and told about a new instrument being built which will have 250 channels.

While there was additional discussion of cerebral blood flow methods, no one presented any evidence to change Dr. Posner's conclusions.

Mr. Bryan Jennett, Professor of Neurosurgery, University of Glasgow, Glasgow, Scotland, presented "Cerebral Ischemia With Head Injury." His observations were based on clinical pathological correlations in 63 cases where there had been head injury and, subsequently, performance of autopsy. He believes that variable perfusion failure resulting from variations in intracranial perfusion pressure is probably responsible for the ischemic changes noted! However, after describing that there was no correlation between prognosis and intracranial pressure, ischemic brain damage and intracranial pressure or brain shift and intracranial pressure, Mr. Jennett realistically concluded that he had been unable to find any satisfactory answer to the real causes of cerebral ischemia in head injury.

Dr. Thomas W. Langfitt, Professor of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania, opened the formal discussion. He believes that cerebral blood flow is influenced by increased intracranial pressure when the latter is high enough. He has made observations concerning 27 comatose patients with head injury and has been able to find some evidence of clinical improvement related to the injection of mannitol, 1 gm/kg I.V. in 10 minutes, although the intracranial pressure was not changed. Dr. Langfitt notes that a favorable change in intracranial pressure is not necessarily a sign of improvement, as it is not nearly always accompanied by a favorable patient clinical course. In further discussion, Dr. Brierley wondered if immediate cardiovascular collapse, at the time of the original injury, which goes essentially undetected, may not be responsible for some of the ischemic brain changes ultimately observed. In any event, the observation that there appears to be no direct relationship between the increased intracranial pressure and the clinical course,
from a therapeutic standpoint, was of considerable interest.

Dr. Russell H. Patterson, Professor of Surgery (Neurosurgery), Cornell University Medical College, New York, New York, presented "Iatrogenic Cerebral Ischemia Following Cardiac Surgery." He related that there are some 75,000 cardiopulmonary bypass procedures performed each year in the United States and that while abnormalities of brain function following such procedures are fairly common, fortunately such abnormalities are mainly transient. Dr. Patterson believes that many of these abnormalities are secondary to the existence of microemboli and has conducted experiments with a variety of filters in the bypass system in an attempt to assess the impact of such microemboli on the brain function of experimental animals (dogs). New filters have been developed and Dr. Patterson hopes that three randomized studies of cerebral function currently under way will assist in further definition of the problem and hopefully solutions will be found.

Dr. J. B. Brierley opened the formal discussion to suggest that reduced perfusion pressure when a patient is put back on his own circulation may be significant in lowering cerebral perfusion pressure to the point where damage to brain structure takes place. Dr. John Moossy, Professor of Pathology, Bowman Gray School of Medicine, Winston-Salem, North Carolina, showed pictures of fibrin thrombi as well as thrombi containing calcium and fat. He pointed out that these may act as emboli and cause complications associated with cardiac surgery. Dr. Geoffrey Evans, Associate Professor of Surgery, McMaster University, Hamilton, Ontario, Canada, warned that silicone coating does not affect the ability of platelets to adhere to surfaces or to one another. Sometimes it is necessary to markedly increase the dose of heparin at the time of cardiac surgery in order to prevent emboli, and he mentioned the use of other drugs to change the physical characteristics of platelets in an effort to prevent thrombus-embolus formation.

The session on Friday, January 7, 1972, was opened with Dr. John S. Meyer, Professor of Neurology, Baylor College of Medicine, Houston, Texas, presenting "The Clinical Management of Cerebral Ischemia." He said that about 80% of nonhemorrhagic strokes are caused by cerebral thrombosis, usually as a result of atherosclerosis of cerebral vessels. Cerebral embolism was the cause of stroke in 15% of the patients with cerebral vascular disease in a recent study in Houston, Texas. The sources of embolism in 42 patients with cerebral embolism were shown and 20 cases had a cardiac source for the embolus. Of these, the most common was a prosthetic heart valve. Dr. Meyer pointed out that an important consideration in the treatment of cerebral embolism is the high incidence of seizures, and anticonvulsant medication is indicated in the acute stages. He has used a slow intravenous infusion of diazepam (Valium) in doses of 5 to 10 mg to control seizures, supplemented with a maintenance dose of diphenylhydantoin (Dilantin), 100 mg three times daily.

While some debate the advisability of treating hypertension in patients with acute or chronic symptoms of cerebral vascular ischemia, Dr. Meyer has shown that measurement of cerebral blood flow and metabolism in "these patients," before and after oral administration of alpha-methyldopa for one or two weeks to control hypertension, revealed that cerebral blood flow increased significantly and cerebral vascular resistance decreased when the blood pressure was lowered. Therefore, it is Dr. Meyer's opinion that cautious reduction of moderate to severe hypertension benefits cerebral hemodynamics by reducing brain edema, decreasing cerebral vascular spasm, and hastening clinical recovery from cerebral ischemic symptoms. He went on to say that he has seen patients with bradycardia caused by digitalis toxicity who had symptoms of cerebral ischemia which resolved completely when cardiac function was improved by reducing the dose of digitalis.

Dr. Meyer emphasized that loss of cerebral autoregulation as a result of brain stem ischemia is common in his experience. Patients with vertebrobasilar insufficiency and signs of brain stem ischemia and infarction had mean arterial blood pressures and cerebral blood flows which were consistently reduced, but in those with hemispheric infarction, impairment of the cerebral autoregulation was less predictable. Dr. Meyer concludes that cerebral autoregulation is impaired greatest in such patients due to ischemic damage to the center of autonomic control of cerebral blood flow in the brain stem and diencephalon. He
believes this may explain the frequent complaints of transient ataxia, vertigo and blurred vision in such patients in the upright position. Treatment should be directed toward preventing or minimizing orthostatic hypotension and increasing cerebral blood flow by the long-term use of cerebral vasodilator drugs. He has found papaverine given orally in doses of 150 mg three times daily to be effective in preventing this form of transient ischemic attack.

Dr. Meyer mentioned that he currently uses the following guidelines regarding the administration of carbon dioxide inhalation in the treatment of cerebral ischemia. (1) Concentrations of CO₂ greater than 5% should not be used and probably should be used with 40% oxygen. (2) Intermittent 5% CO₂ inhalation may be beneficial in patients with TIAs and in mild and moderate cerebral infarct but is contraindicated in the acute stage of intracerebral hemorrhage and in massive cerebral infarction. (3) Since the “intracerebral steal” has been reported only during the early stages of brain infarction, it is now Dr. Meyer’s practice to defer 5% CO₂ inhalation for the first 48 hours after moderately severe cerebral infarction and to use 40% oxygen inhalation during this interval.

Dr. Meyer told the members of the Conference that cerebral edema is a consistent complication of cerebral infarction and is a major cause of death during the acute stage. Reported mortality rates following cerebral infarction vary during the first week from 22% to 48%! In Dr. Meyer’s stroke center effective treatment with hyperosmolar agents such as glycerol and mannitol have been evaluated in animals and in humans. Both of these agents were found to reduce cerebral edema and measurably decrease intracranial pressure while increasing cerebral blood flow. When Dr. Meyer administers glycerol intravenously, he infuses 500 ml of 10% glycerol in a solution of 5% glucose or normal saline over a period of three to four hours daily for the first four or five days of acute cerebral infarction. Dr. Meyer has reported that in a prospective therapeutic trial involving 36 selected patients with acute cerebral infarction, the mortality in the first week was only 12%, which is significantly lower than that reported in the literature. Steady improvement of neurological status occurred in all of the patients (except those quadriplegic and comatose where the treatment was started) during and at the completion of four days of treatment.

Dr. Meyer mentioned that previously he along with others reported the beneficial effects of intravenous administration of low-molecular-weight dextran in the treatment of acute cerebral infarction. This treatment is contraindicated when the possibility exists of precipitating acute renal failure in patients with impaired renal function and precipitating heart failure in patients with impaired cardiac function.

Dr. Meyer recommended the use of papaverine in the acute stage of cerebral infarction and the long-term oral treatment in patients recovering from completed strokes and transient ischemic attacks in the vertebrobasilar territory and in patients who were not suitable candidates for surgical excision of plaques in the cervical portion of the carotid arteries. Another vasodilator, hexobendine, produced a statistically significant increase in hemispheric blood flow in regional cerebral blood flow when comparison was made with another group of patients who had received a placebo. There were also measurable clinical improvement and increased cerebral blood flow in the patients getting the hexobendine.

Dr. Meyer reported that his experience confirmed that of Patten and his co-workers that steroids are usually effective in bringing about rapid recovery and reducing mortality rates in the acute stage of cerebral infarction; however, because steroids cause side effects, such as gastric ulceration and hemorrhage, and the effect of steroid is less rapid, Dr. Meyer prefers glycerol in treating such patients.

Formal discussion was opened by Dr. Olaf Paulson who noted that apparently there had been no significantly beneficial effect of either hypercarbia or hypocarbia when either was used in the treatment of patients with acute cerebral infarction.

Formal discussion was continued by Dr. Peritz Scheinberg, Professor of Neurology, University of Miami School of Medicine, Miami, Florida, who reviewed the problems of clinical definition of the type and stage of stroke which an investigator might be discussing at any given point in time, and the complexities of the pathogenesis of the damage to neuronal function; he concluded that in the
light of his experience he agreed with "clinicians of prior generations" that when significant cerebral infarction has occurred he does not see any evidence that any method of treatment significantly benefits the actual cerebral infarct and therefore the ultimate neurological function of the patient. He went on to emphasize the importance of all aspects of preventive medicine as we literally try to decrease the impact of the stroke problem. Dr. Scheinberg believes that there are measures which can be applied today which will help in reducing the morbidity and mortality of stroke but exhorted the members of the Conference to look with scientific skepticism on the wide variety of methods of treatment for acute cerebral infarction.

The formal discussion was completed by Dr. C. H. Millikan, who joined Dr. Scheinberg in declaring that there is tremendous variation in the natural history of cerebral infarction and that the problems of this variable natural history are intensified to the individual attempting to assess a new treatment because of the different duration of time elapsing between the onset of the stroke and the initiation of the treatment. He pointed out that in some of the data presented 72 hours had elapsed between the onset of the stroke and the beginning of treatment, while in other instances the minimum duration of the interval was six days! In the latter instance the time period during which cerebral edema ordinarily is an important factor was already past when the treatment was started and, in fact, when treatment was delayed for 72 hours the primary issues about the outcome of the stroke had already been joined.

There is great variation in natural history of acute infarction in the carotid system—in the 204 consecutive patients previously reported by the Mayo Clinic group, the mortality rate was 14, while at the end of a two-week period of observation, 12% of the patients were normal! The remainder had varying degrees of neurological deficit. When carbon dioxide therapy was used in a similar group of patients, there was no statistically significant improvement in the outcome.

Dr. Millikan agreed with Dr. Scheinberg in stating that in the experience of the Mayo Clinic group there was no clinical evidence that carbon dioxide treatment, stellate ganglion block, low-molecular-weight dextran, and vasodilators, such as papaverine and hexobendine, significantly changed the natural history of acute cerebral infarction.

The role of anticoagulants in preventing the worsening of progressing cerebral infarcts and in preventing cerebral infarcts in patients with transient ischemic attacks was reviewed at the Fourth Princeton Conference on Cerebral Vascular Diseases and, therefore, was not discussed at the present meeting.

Dr. Raymond Bauer, Professor of Neurology, Wayne State University School of Medicine, Detroit, Michigan, reported completion of a controlled study of the use of steroids in patients with acute cerebral infarction and noted that there was no apparent neurological difference in the treated and untreated groups of patients. He added that the problems with gastrointestinal bleeding had actually occurred in the patients not receiving dexamethasone!

Under a general topic of "Aids in Diagnosis" Dr. Herbert Goldberg, Director of Neuroradiology, Stroke Research Center, Philadelphia General Hospital, Philadelphia, Pennsylvania, presented a series of slides of arteriograms which had been magnified times two. He was particularly interested in demonstrating narrowing, tortuosity and occlusive lesions of the penetrating branches of the middle cerebral artery and was able to present convincing demonstrations of these lesions. He also showed some slides of angiotomograms to further define these lesions. Dr. H. L. Baker, Jr., Division of Radiology, Mayo Clinic, Rochester, Minnesota, showed slides of two times magnification angiograms of the circulation around the sella turcica and pituitary gland.

Dr. D. Gordon Potts, Professor of Radiology, Cornell University Medical College, New York, New York, presented diagrams and pictures of equipment to perform circular angiotomograms. He suggested that this special examination should be considered if there is (1) strong suspicion of a brain lesion but conventional angiograms are normal, (2) the plain x-rays are abnormal but the conventional angiograms are normal, (3) that abnormality is demonstrated in either the angiograms or the plain films but further information is needed, (4) full demonstration of avascular regions, (5) demonstrations of areas of small increases of vascularity, (6) demonstration of arteries or veins obscured by other vessels, and (7)
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demonstration of vascular structures in the posterior fossa.

Dr. Mannie Schechter, Professor of Radiology, Albert Einstein College of Medicine, Bronx, New York, gave some preliminary comments about tomoscopy which will permit fuller visualization of vessels in space and hopefully will be well enough developed for clinical use within the relatively near future.

Dr. Norman Chase, Professor of Radiology, New York University Medical College, New York, New York, discussed the "Radiographic Diagnosis of the Ulcerative Atherosclerotic Plaque." He reviewed some of the technical difficulties in correctly producing films which will permit differentiation of atherosclerotic and ulcerative atherosclerotic lesions. Among the slides of angiograms presented was one of a filling defect in an ophthalmic artery. He also had some examples of sequential angiography in which there was evidence of an occluding lesion which disappeared when angiograms were taken a few days later. As a formal discussant, Dr. Thomas H. Newton, Professor of Radiology, University of California, San Francisco, California, added that most ulcerative lesions occur along the posterior wall and that the radiologist must be very careful to avoid false negative diagnoses. Dr. Newton believes that the incidence of ulceration is higher than usually stated.

"The Use of the Gamma Camera in Cerebrovascular Disease" was reviewed by Dr. Richard Janeway, Professor of Neurology, Bowman Gray School of Medicine, Winston-Salem, North Carolina. He described the history of the development of the camera, its present state and the use of "dynamic studies" which double the yield compared to the rectilinear scan. Dr. Janeway believes that there should be continued development of the camera as a possible method of measuring regional cerebral blood flow.

Dr. Henry Wagner, Professor of Radiology, Johns Hopkins College of Medicine, Baltimore, Maryland, discussed the use of such equipment and stressed the hope that the gamma camera could become a method of evaluating therapy. He never made clear how this was to be accomplished. In subsequent discussion, Drs. Paulson and Waltz both pointed out that it is still necessary to perform an angiogram in patients where there is a serious question about differential diagnosis or where vascular surgery is to be done.

The final portion of the Conference was devoted to the presentation and discussion of material concerning blood platelets. Dr. Ralph Nachman, Associate Professor of Medicine, Cornell University Medical College, New York, New York, reviewed the physiology of platelets and called attention to the similarities to exudative polymorphonuclear leukocytes which suggest that platelets can act as inflammatory cells; certainly platelets contain substances which can change vascular permeability. It was emphasized that platelet aggregation can occur with an intact intima.

Dr. Marjorie Zucker, Professor of Pathology, New York University College of Medicine, New York, New York, discussed the "Pharmacology of Agents Which Affect Platelet Adhesiveness and Aggregation." She turned her attention principally to acetylsalicylic acid (aspirin) and dipyridamole (Persantine). In some fashion the release of ADP by platelets is affected, although the ultimate mechanism by which platelet aggregation is decreased is not fully understood.

Dr. Paul Didisheim, Department of Clinical Pathology, Mayo Clinic, Rochester, Minnesota, was prevented by illness from opening the discussion; however, Dr. J. P. Whisnant read Dr. Didisheim's comments. Dr. Didisheim mentioned that a drug, pyridanolcarbonate (Anginin), also decreases the characteristic of the platelets to aggregate and may ultimately be of some clinical interest.

Dr. Geoffrey Evans made the final presentation of the Conference with "The Clinical Effects on Symptoms of Cerebral Ischemia by Agents Which Affect Platelet Adhesiveness." After some discussion of the relative actions of acetylsalicylic acid, sulfinpyrazone (Anturane), and dipyridamole (Persantine), Dr. Evans described clinical trials of treatment in 20 patients said to have transient ischemic attacks. However, 17 of the patients only had amaurosis fugax and all patients with 70% or greater stenosis of a carotid artery had been taken out of the series and had surgical reconstruction of the appropriate carotid artery. The study was conducted by recording the mean number of attacks per week under varying circumstances, the patients receiving either a placebo or sulfinpyrazone. The patients
had fewer attacks when receiving the sulfinpyrazone than when they were receiving the placebo.

Dr. Marion I. Barnhart, Professor of Physiology, Wayne State University, Detroit, Michigan, told about some of her observations on the morphology of platelets under a variety of circumstances. Finally, Dr. William Hass, Professor of Neurology, New York University College of Medicine, New York, New York, reminded the listeners of a controlled clinical study in Finland which suggests that regular ingestion of aspirin is of no benefit in the prevention of thrombosis.
Summary of the Eighth Princeton Conference on Cerebral Vascular Diseases, January 5-7, 1972, Nassau Tavern, Princeton, New Jersey

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