Summary of the Tenth Princeton Conference on Cerebral Vascular Diseases, January 7–9, 1976

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Chairman of the Conference: Peritz Scheinberg, M.D.
Vice-Chairman of the Conference: Erland R. Nelson, M.D.

FOLLOWING REMARKS by Dr. Scheinberg, a presentation, “Frequency and Symptom Analysis of Transient Ischemic Attacks: A Cooperative Hospital Study,” was given by Dr. Mark L. Dyken (Professor and Chairman, Department of Neurology, Indiana University Medical School, Indianapolis, Indiana). In the limited time available, Dr. Dyken could present only some general comments concerning the 512 transient ischemic attack (TIA) patients collected during 21 months' time in the various centers; the average interval of follow-up apparently was 14.3 months. The study was designed to determine the current medical practice in handling TIA and the reliability of diagnosis and to compare varieties of therapy. Four hundred patients had carotid TIAs and 112 had vertebralbasilar attacks. There was high blood pressure in 52% of the group and ischemic heart disease in 36%. Bruits (not defined) were noted in 289 patients, and of these only 67 were appropriate to the side of the symptoms. Retinal artery pressures were obtained in only 20% of the patients but were abnormal in 94% of those studied. Approximately 27 patients had retinal emboli; apparently the examination for these was infrequent, as was obtaining retinal artery pressures. Four hundred sixty-four patients had angiographical study; 81% of these had abnormal angiograms and 50 patients had occlusion of a carotid artery. It is presumed that the neurological examination was negative, although the traditional definition of TIA was being used. There was no significant difference in any of the treatments and it was not mentioned how the patients were selected for the different modes of therapy. In the discussion of this paper, Dr. Herbert R. Karp (Professor of Neurology, Emory University School of Medicine, Atlanta, Georgia), who had access to and was able to study the data, presented tables and graphs showing the extraordinary variation in the types of data obtained in the different participating institutions. He commented that he believed it completely scientifically unwise to pool all of this variable material and point to any averages as a result. Dr. Karp added that he had come to the position of believing it was more sensible to look at the observations from one institution or one department or those made by one knowledgeable person, in contrast to simply pooling large quantities of data from entirely different sources.

Dr. H. J. M. Barnett (Professor and Chairman, Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada) reviewed the current notions about the pathogenesis of focal transient cerebral ischemic attacks. These include thrombus-emboli, transient decrease in systemic blood pressure with a distal atherosclerotic stenotic brain vessel, transient hypoglycemia with the same distal arterial pathology, anemia, polycythemia, and shunting. He stressed particularly the probable cardiac cause of TIA and mentioned the problem of the “prolapsing” mitral valve syndrome as a cause of embolic events and the possibility that some attacks are caused by emboli arising from stumps of occluded arteries. In the discussion, there was some question about the fashion in which this diagnosis of TIA was validated.

Dr. James F. Toole (Walter C. Teagle Professor of Neurology, Bowman Gray School of Medicine, Winston-
Salem, North Carolina) discussed an aspect of treatment of TIA patients. He believes that a recent transient ischemic focal cerebral attack constitutes an emergency and suggests that intravenous heparin be given promptly after a patient is admitted to the hospital. Patients admitted with TIA all should have angiograms as soon after admission as possible. Coumadin should be used for long-term therapy. Dr. Toole recommended reconstruction of carotid arteries by thromboendarterectomy if an appropriate lesion was detected. He related that more patients who have transient focal cerebral ischemic attacks die of cardiac lesions than of stroke. Dr. Toole described two patients with clots at the origin of the internal carotid artery. At the time of surgery, there was no atherosclerosis at the site of the lesion. (Dr. F. William Blaisdell, Chief of Surgery Service, San Francisco General Hospital, San Francisco, California, commented later that perhaps these were very large emboli.) The exact nature of this type of carotid obstruction was not fully solved. Dr. Toole later commented on the growing experience with temporal artery bypass surgery for stroke and emphatically pointed out the very great need for a comparative randomized study of patients undergoing superficial temporal artery to middle cerebral artery bypass. Dr. O. Howard Reichman (Associate Professor of Surgery, Loyola University Medical Center, Maywood, Illinois) (later in the meeting) agreed with this and has designed a protocol for a cooperative study.

Dr. William S. Fields (Professor and Chairman, Department of Neurology, University of Texas Health Sciences Center, Medical School, Houston, Texas) briefly reported some of the experiences of the Cooperative Study of Aspirin for the treatment of transient focal cerebral ischemic attacks. He stated that for patients having had one attack there was no difference between treated and untreated patients in occurrence of further attacks and cerebral infarction, but for patients having had multiple TIAS there appeared to be a better "result," i.e., fewer strokes, among the patients receiving aspirin than in those not receiving aspirin. Dr. Barnett commented on the Canadian Cooperative Study of TIAS which involves comparisons between several treatments, including antiplatelet agglutinating agents. He reported that their statistics to date had been carefully reviewed and that the results appeared to be inconclusive.

The Thursday morning session was devoted to "atherosclerosis." Dr. Robert W. Wissler (Donald N. Pritzker Professor of Pathology, University of Chicago, Chicago, Illinois) introduced the topic by giving a review of our understanding of atherosclerosis and its development. He concluded by stating that atherosclerosis could be controlled and even reversed if by diet humans could control hypercholesterolemia and hyperlipidemia.

Dr. Donald L. Fry (Chief, Laboratory of Experimental Atherosclerosis, National Heart and Lung Institute, Bethesda, Maryland) presented evidence that high blood pressure changes the permeability of the endothelium of arteries to substances (including lipid). He demonstrated that there was an increased stress (force per unit of area) caused by the actual high blood pressure which in turn had a special effect on gradients of exchange across the endothelium of the artery, especially for lipids. Dr. Fry believed if the endothelial surface was damaged at all by arterial injury that these forces had an increasingly significant importance.

Dr. Erland Nelson presented data on "Ultrastructural Changes in the Endothelium With Atherosclerosis." He discussed the interaction which takes place between a platelet or several platelets and the endothelium. This interaction potentially constitutes "damage" to the endothelium which is particularly likely to occur at branch points in vessels, where there is mechanical flow trauma. Dr. Nelson demonstrated that the administration of heparin was helpful in preventing this kind of "damage." He also was able to show that there were increasing gradients of damage in animals hyperlipemic (high cholesterol) at the time of study. Dr. Nelson demonstrated an extraordinarily interesting phenomenon — using scanning electron microscopy, he showed that platelets collected in areas of arterial spasm, that endothelial cells were damaged proximal to the region of spasm, and that damaged areas were covered with collections of platelets. He showed one photograph where a thrombus was beginning to form on such a base.

During the discussion period a question was asked concerning the relationship between "fatty streaks" and "fibrous plaques." Dr. John Moossy (Professor of Pathology and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania) pointed out that no one has ever proved any "non-correspondence" between the existence of "fatty streaks" and "fibrous plaques!"

Dr. Russell Ross (Professor of Pathology, University of Washington School of Medicine, Seattle, Washington) discussed "The Role of Smooth Muscle and Platelets in Atherosclerosis." Smooth muscle proliferation is the sine qua non of atherosclerosis. Arterial smooth muscle cells in culture are stimulated to grow by low density lipoproteins, platelets and plasma. A factor in platelets seems to be the most effective growth-stimulating factor. He commented that if smooth muscle cell proliferation did not occur there would be no arterial lesions. Slides were shown of experiments conducted on baboons presenting convincing evidence that lesions produced in arteries by physical trauma were fully reversible in six months' time if the animals were on a normal diet, but animals on a high lipid intake had lipid-containing lesions six months after the same initial trauma to the vessels. Dr. Ross added that the administration of diprydamole (Persantine) inhibits smooth muscle proliferation but the administration of the drug does not protect the endothelium to prevent atherosclerosis if the animals are on a high lipid intake. He believes it wise to keep the blood pressure normal, keep the blood lipid levels normal, and avoid platelet adherence in an effort to eliminate the complications of atherothrombosis.

Dr. William E. Connor (Professor of Medicine, Health Sciences Center, University of Oregon, Portland, Oregon) reported on "Dietary Lipids, Hyperlipidemia, and Atherosclerosis." He emphasized that every effort should be made to keep blood lipids low at all age ranges, as the death rate from atherosclerosis is clearly related to cholesterol intake. Dr. Connor believed that children and young adults should have a blood cholesterol level less than 180 mg %, 25 to 45-year-old adults under 200 mg %, and those more than 46 years of age less than 220 mg %. He pointed out that the
chsholesterol molecule cannot be easily metabolized and that there is a constant flow of cholesterol in and out of atheroma. He said that with low serum cholesterol levels in experimental animals, atheromas shrink. Dr. Donald Tower (Director of National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland) raised questions about the relationship between the intake of cholesterol in the diet and its relationship to the blood cholesterol. The natural history of cerebral infarction in animal which shows that after one hour's duration of transient ischemia, brain amine levels fall but norepinephrine stays constant if the rat is on a respirator.

The general topic for the Thursday afternoon session was "Neurotransmitter and Stroke." Because of the complex nature of these chemical studies, the work described is thus far limited to observations concerning experimental animals in the laboratory (gerbils, rats, cats, monkeys and baboons).

In introducing the topic for the afternoon, Dr. Davis commented on the importance of neurotransmitter receptors in stroke from a theoretical point of view.

Dr. Richard J. Wurtman (Professor of Endocrinology and Metabolism, Massachusetts Institute of Technology, Cambridge, Massachusetts) discussed "Acute Stroke and Monoamines," describing phenomena occurring when stroke was produced in gerbils. When a stroke is produced in experimental animals, neurotransmitters are released which may have widespread effects, some of which are deleterious for cerebral metabolism and circulation. Oxygen lack in the infarcted area impairs the deactivation of neurotransmitters released in the tissue. Reserpine may protect the brain during infarction in experimental animals as the tissue energy potential does not drop in animals given this substance before an experimentally produced infarction. Dr. Wurtman emphasized that there are still unanswered questions: "Does release of transmitters from damaged neurons act on other blood vessels causing spasm and extending the area of ischemia?" and placed particular emphasis on the question, "What really happens in human stroke?"

In opening the discussion, Dr. Scheinberg reminded the attendees that in stroke in the rat (produced by emboli), dopamine increases for the first four hours while norepinephrine stays constant if the rat is on a respirator.

Dr. Scheinberg again mentioned that introducing aminophylline into this set of variables seems to produce a beneficial reaction — an intriguing notion. Dr. K. M. A. Welch (Assistant Professor of Neurology, Baylor College of Medicine, Houston, Texas) mentioned experience in the experimental animal which shows that after one hour's duration of transient ischemia, brain amine levels fall but norepinephrine appears to be less sensitive to the effect of hypoxia than dopamine. During the discussion, Dr. Wurtman raised a question about the natural history of cerebral infarction in patients on long-term phenothiazine therapy. No one was able to report such experience.
to have a stroke over the number answering yes to the question) was 80 in Japan, 70 in Honolulu and 71 in San Francisco. Dr. Kagan noted that high blood pressure was related to all types of stroke, while cholesterol levels appeared to be increased in patients having coronary artery disease; however, the relationship to stroke was not clear-cut. Dr. Kagan reported that there was definite evidence that stroke was more common in Japanese in Japan than in Japanese in Honolulu or in San Francisco. He added that small vessel (brain) sclerosis was more common in Japan than in Honolulu. Dr. Kagan remarked that for four years he and his colleagues studied 124 patients (prospectively) with neck bruits. Four of the 124 patients (less than 1% per year) had a stroke. Subsequently, Dr. Burton A. Sandok (Associate Professor of Neurology, Mayo Medical School, Mayo Clinic, Rochester, Minnesota) mentioned that it is important to precisely define the position and nature of the bruit. Dr. Kagan responded that of the four patients having a stroke, one bruit was supraclavicular, two were over the carotid arteries, and one was "soft." Of the patients having stroke, 25% had some form of intracranial bleed, 71% had cerebral infarction, and 4% were classified as "other." There did not seem to be any significant difference in the percentages of intracranial hemorrhage in Japanese in Japan and Japanese in Honolulu.

The remainder of the morning was spent concerning surgical consideration of subarachnoid hemorrhage and cerebral infarction. Dr. Charles G. Drake (University Hospital, London, Ontario, Canada) commented on 321 cases of ruptured intracranial aneurysm treated surgically, dividing these into 213 patients with small aneurysms, 54 with giant aneurysms, and 54 with posterior circulation aneurysms. Seventy-four percent of the patients with small aneurysms had an excellent result; 60% of those with giant aneurysms and 37% of those with posterior circulation aneurysms had a similar outcome. Dr. Drake mentioned that 18% of the total patients died of rebleeding before surgery was performed. Twenty-five of the 321 patients died, a mortality of 7.7%. Dr. Drake reported that vasospasm remained a serious problem. Subsequently, in the discussion Dr. Joseph Ransohoff (Professor and Chairman, Department of Neurosurgery, New York University School of Medicine, New York, New York) reported that Isuprel plus aminophylline was used with good results for treating vasospasm associated with acute subarachnoid hemorrhage secondary to ruptured aneurysm. Dr. Ransohoff added that he thought the spasm problem had not been solved but was hopeful. Dr. Nicholas T. Zervas (Associate Professor of Neurosurgery, Harvard Medical School, Beth Israel Hospital, Boston, Massachusetts) had only a brief amount of time in which to mention that a double-blind randomized study concerning cerebral vasospasm and subarachnoid hemorrhage was being conducted in Boston. One hundred six of 135 patients have been operated upon and Dr. Zervas described a delayed neurological deficit developing in 13 such patients. Ten of these had angiographical study and eight showed vasospasm.

Dr. Reichman reported on the status of "Neurosurgical Microsurgical Anastomosis for Cerebral Ischemia." His indications for the operation were middle cerebral artery occlusion with TIAs, middle cerebral artery stenosis with reversible ischemic neurological deficit, bilateral carotid occlusion with TIAs, intracranial carotid stenosis or occlusion with TIAs, as well as some less significant items, such as giant aneurysm and small branch occlusions. Dr. Reichman had performed the operation on 78 patients and, in many of them, had been able to document an increased rate of flow in the territory supplied by the surgically anastomosed vessels. Dr. Reichman emphatically recommended that a collaborative study of superficial temporal-middle cerebral branch artery bypass be gotten underway with randomized selection of patients. Dr. George Austin (Professor of Neurological Surgery, Loma Linda University, Loma Linda, California) mentioned that he also had performed the operation on 84 patients. Dr. Austin stated that there was increased perfusion and an increased metabolic rate in the territory supplied by the reconstructed vessels.

"The Aging Process" was the general topic for the remainder of the Conference. "Theories of Aging" were discussed by Dr. Leonard Hayflick (Professor of Medical Microbiology, Stanford University School of Medicine, Stanford, California). He pointed out that there is an estimated 0.8% loss of function per year from age 30. He pointed out that life expectancy changes have been changed most by improvement in health from birth to middle age rather than at the older end of the scale. "Morphology of the Aged Brain" was presented by Dr. Robert D. Terry (Professor and Chairman, Department of Pathology, Albert Einstein College of Medicine, Bronx, New York). Dr. Terry pointed out that changes in the brain associated with aging are similar to those seen in Alzheimer's disease and not those seen with atherosclerotic cerebrovascular disease. Intracellular lipid deposition and the presence of neurofibrillary tangles are the usual alterations, not areas of infarction. He also pointed out that these changes are similar to those found with scrapie which suggests a potential viral etiology for senility. "The Biochemistry of Aging" was given by Dr. Dennis J. Selkoe (Instructor in Neurology, Harvard Medical School, Children's Hospital Medical Center, Boston, Massachusetts). Dr. Selkoe reported that there are no convincing protein, lipid or neurotransmitter changes in neural tissue associated with aging. No material was presented which related directly to the diagnosis or treatment of human cerebrovascular disease.
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