Summary of 12th Conference on Cerebrovascular Disease

Williamsburg, Virginia, March 2–4, 1980

Fletcher H. McDowell, M.D., and Clark H. Millikan, M.D.

The 12th Conference on Cerebrovascular Disease was held in Williamsburg, Virginia, March 2–4, 1980. The first session of the Conference was devoted to a review of functional imaging of the brain with in vivo biochemical and perfusion studies. The initial presentation was "Scanning Systems and Analytical Methods using Positron Emission Tomography" given by Dr. Marcus E. Raichle of the Washington University School of Medicine, St. Louis MO. He described current detector isotope strategy mentioning that oxygen-15, nitrogen-13, carbon-11 and fluoride-18, which have half-lives of 2, 10, 20 and 110 minutes respectively, were the radioactive substances currently in use. The detector resolution capability is about 6.0 mm at present and the theoretical lower limit of resolution is about 1.5 mm. Sodium iodide detectors are commonly used but more sensitive detectors, such as those made with bismuth germanate and cesium fluoride, are being developed.

Dr. Raichle reported that brain blood volume, cerebral metabolism, tissue chemical composition, cerebral blood flow and the permeability of the blood-brain barrier can be measured by positron emission tomography. He reviewed the details of measurement of cerebral blood flow with a PET scanner and showed examples of scans using H2O15 in patients with stroke. He reported that there are now available many radio-labeled pharmaceuticals whose action and localization can be traced through the central nervous system. Utilization and consumption of metabolites can be measured using radioactive oxygen in water or in carbon dioxide.

Functional mapping of metabolism in the brain using positron emission tomography in animals was discussed by Dr. Martin Reivich of the University of Pennsylvania. He commented that there are very tight spatial links between function and anatomy in the rat; stimulating one whisker can cause a localized increase in blood flow and cerebral metabolism as demonstrated by the autoradiographic appearance of the rat brain. Dr. Reivich discussed his experience using fluorodeoxyglucose to study visual, tactile and auditory stimuli and their effect on local cerebral metabolism in man. In 6 human subjects, visual stimuli were applied to the left visual field which immediately produced a higher metabolic rate in the right visual cortex and when the right visual field was stimulated, the left visual cortex showed increased blood flow and metabolism. Tactile stimuli to one hand was accompanied by an increase of blood flow and metabolism in localized areas of the cerebral cortex in the contralateral sensory areas. Auditory
stimuli, when applied to the left ear, showed changes in blood flow and metabolism in the right auditory cortex. Dr. Reivich reported that now it was possible to map the cortex indicating precise functional areas by using the PET scanner with external stimulation.

Metabolism and Blood Flow

Dr. Robert Ackerman of the Massachusetts General Hospital reported his experience studying oxygen metabolism and blood flow using positron emission techniques. Cerebral blood flow was studied using radioactive carbon dioxide. The metabolic requirements for oxygen with O₁₆ and glucose were determined. He noted that positron emission tomographic scans can indicate changes in cerebral metabolism following stroke, often showing changes which preceded those visible on the CAT scan. He found that changes in cerebral blood flow evolved in a patchy fashion and that blood flow changes correlated less well with what was believed to be going on in the brain following stroke. Also, hyperemia may not reflect increased metabolism. In correlating changes in cerebral blood flow, cerebral metabolism and the oxygen extraction fraction, Dr. Ackerman reported that he believed that when the oxygen extraction fraction remains high, even though the cerebral blood flow is decreased, the prognosis for stroke is better than if the oxygen extraction fraction and cerebral blood flow stay down. He said that oxygen utilization was more consistent in indicating changes in tissue than was blood flow, as there was often an increase of blood flow with hyperemia due to vasodilatation. Later, if hyperemia occurred or increased, it was due to blood flow through an increased number of capillaries but was not nutritional flow.

Dementia and PET

Dr. Tibor Farkas of the New York University Medical College reported on the study of dementia and mental disorders using positron emission tomography. In a study in which he had used 18-fluorodeoxyglucose in a patient with untreated schizophrenia, there was little or no evidence of metabolism in the frontal cortex. He then showed that after the patient had been placed on neuroleptic agents, the frontal cortex began to show metabolic activity. When a placebo was used, there was again lack of metabolism in the frontal lobe. He reported that in his studies of patients with dementia the cerebral metabolic rate was 50% lower than in controls, with the principal area of lower metabolism in the frontal lobes.

In the discussion following these 2 papers, Dr. Nils Lassen of the Bispebjerg Hospital, Copenhagen, said he had developed equipment which allowed him, following use of inhaled radioactive xenon, to produce tomographic slices through the brain using apparatus similar to that used for the CAT scan. He demonstrated that using these techniques local changes in blood flow and function can be measured.

Dr. Lindsay Symon of the National Hospital, London, raised the issue of the temporal profile of measurements for each of the isotopes used. He pointed out that there was interest in this problem because the half-life of isotopes varies and the usefulness of measurements using different isotopes declined with decreasing half-life.

Dr. Arthur Waltz of the Pacific Medical Center, San Francisco, pointed out that there were 2 types of hyperemia associated with cerebral infarction, one that occurred early with increasing cerebral blood flow, which may cause edema, and the other which occurred later with an increase in flow. This was probably due to a physical change in vascular structure.

Alzheimer's Disease

Dr. David Ingvar, University of Lund, Sweden, demonstrated his studies on patients with Alzheimer's disease using inhaled radioactive xenon to measure cerebral blood flow. He found a considerable decrease in average local cerebral blood flow in both cerebral hemispheres with varying distributions of decrease in flow depending on the type of dementia. Cerebral blood flow was generally low frontally or low in the post-central regions. In his study of 40 patients with schizophrenia, there was a decrease in blood flow in the frontal region in 13. He said he believed that there was less activation of local cerebral blood flow in patients with schizophrenia after application of external stimuli such as pain and pinprick. Dr. Ingvar reported that he had found an increase in frontal blood flow in patients with manic depressive affective illness.

Dr. Bruce Schoenberg of NINCDS, Bethesda, asked how much variation occurred in the measurement constants in CAT scanning. He asked whether one could safely move from one species to another species and if one moved from species to species in experiments, whether the so-called "lump constant" remained the same.

Dr. Raichle replied that one cannot move from species to species easily and the "lump constant" must be recalculated each time one uses a different animal.

Dr. Ginsberg, University of Miami, asked how early an oxygen utilization change occurred in transient ischemic attacks. Dr. Ackerman pointed out that the earliest patient he had studied was at 20 hours after a TIA and that, generally, patients with transient ischemic attacks were functionally normal at that point.

Diagnostic Procedures

The second session of the Conference was devoted to diagnostic procedures in cerebral vascular disease. The first report was given by Dr. William Feindel, Montreal Neurological Institute, who discussed physiological tomography with positron emitting tracers which allow study of cerebral blood flow and metabolism. Dr. Feindel said he was using different positron emitters, including gallium-68 and krypton-57, which had a high positron output. Using germanate detectors, which are more sensitive than
sodium iodide detectors, and mounting 32 such detectors in 2 rings, he was able to measure cerebral blood flow. He found a blood barrier breakdown in the patients with stroke. His techniques were useful in following changes within the brain after extracranial/intracranial artery bypass. He said he believed the methodology developed at the Montreal Neurological Institute would be useful in studying the cerebral metabolism of patients following stroke and recording restoration of blood flow after various arterial operations.

Dr. Eric Fossel, Department of Biophysics, Harvard Medical School, discussed nuclear magnetical resonance as a means of detecting metabolic changes in the brain. He mentioned that the advantages of this technique were that it was three-dimensional, it did not require radiation, and could make local measurements of metabolism. He had been investigating metabolic change in focal cerebral ischemia using phosphorous-31 and found that during reversible cerebral ischemia cerebral blood flow was reduced or absent, and ATP and phosphorus were reduced. During potentially reversible cerebral ischemia, cerebral blood flow and ATP were absent and phosphorus increased. During irreversible ischemia, cerebral blood flow, ATP, and phosphorus were absent. He reported that the magnetic fields were used to determine a nuclear magnetic resonance spectrum. Translating these changes into an image did not harm animals and the method had been used on human beings without problems. He pointed out that nuclear magnetic resonance imaging could provide an anatomical demonstration with a very high resolution. He did not show any illustrations of human central nervous system tissue. Dr. Fossel, in answer to questions, said that it would be possible for nuclear magnetic resonance techniques to image neurotransmitters. He also said that he thought it would be possible to image lithium in the brain. Questions were raised about the resolution possibilities of magnetic resonance, and Dr. Fossel replied that it would probably be greater than that of a PET scanner. Asked whether magnetic resonance studies were safe, he said that they were.

Non-Invasive Imaging

The next session of the conference was a review of non-invasive carotid imaging using, in general, ultrasonic procedures. Dr. Burton Sandok of the Mayo Clinic Medical School reviewed the applicability of remote measurements such as blood pressure in the eye or from the surface of the eye using ophthalmodynamometry, recording pulse pressure over the eyes and looking for differences between pulsations in the 2 eyes. He said that these measurements were limited in usefulness.

He reviewed direct non-invasive imaging which involves phonographic or ultrasound assessment of flow at the carotid artery bifurcation, using B-scanning ultrasound imaging. He demonstrated that Doppler techniques can detail differences in the rate of flow at pre and poststenotic sites and produce an accurate image of the carotid bifurcation. With sound amplification, scans can detect not only the degree of stenosis but they can give some evidence of atherosclerotic plaque ulceration. Scans are technically unsatisfactory in 5% of the patients and one of the problems is that thrombus in an artery may be difficult to distinguish from blood. Generally, he believed that ulcers cannot be visualized with high accuracy. In clinical trials, when ultrasound was compared to angiography, the non-invasive testing procedures are accurate in only 2 out of 3 patients. With Doppler techniques, they are more accurate, reaching about 100% accuracy in outlining a normal artery. Occlusion detection is about 75% accurate and stenosis determination varies from 50% to 95% accurate. False positive and false negative rates are relatively high. He concluded that these techniques are generally good in detecting severe disease but with minimal disease, detection is poor.

Dr. Sandok reviewed the use of spectral sound analysis which he believed was fairly accurate but is less reliable in detecting low degrees of stenosis. Ultrasound scanning and a determination of flow velocity seem to be the most accurate methods in detecting carotid stenosis. With all of these techniques, however, there was a potential false positive rate of about 10% and a false negative rate of about 20%. Dr. Sandok concluded that at this time they cannot substitute for angiography in determining whether or not surgical treatment of an arterial lesion is warranted but the techniques were useful as supplementary diagnostic tools.

The discussion of this problem, prepared by Dr. Mark Dyken of Indiana University Medical School, was read by Dr. Sandok. The summary of his comments indicated that for all of these ultrasonic diagnostic techniques, none was able to rule out or replace cerebral angiography.

133Xenon Inhalation

Dr. John Stirling Meyer of Houston then reviewed the status of the 133-xenon inhalation techniques and the stable xenon techniques in the measurement of cerebral blood flow. He pointed out that inhalation using radioactive xenon is safe, that normal values for all ages are available and that it is a well-established technique. It can determine blood flow in gray matter as well as white matter and the cost for performing the study is reasonable. Its disadvantage is that it does not distinguish pathologic from normal tissue and that the lambda values or the partition coefficients are not known and that extracranial circulation may be a variable contaminating factor which is difficult to determine.

He indicated that the stable xenon technique is valuable in that most institutions now have a CT scanner and that the resolution of this method is good at one millimeter. He pointed out that zero flow in tissue can be identified and that regional flow values can be determined. Dr. Meyer concluded that the use of stable xenon with transmission scanning will become a useful diagnostic technique.
Dr. Meyer was asked about the duration of a scan and replied that scanning time is approximately one minute. It took only one or 2 days of training to educate someone to carry out scans.

Dr. Schoenberg asked Dr. Sandok about the experience required in interpreting audio signals in using the pulse Doppler system. Dr. Sandok answered that considerable experience was required and that a lack of experience might be an important factor in the accuracy of these tests.

Dr. Charles Olinger of the University of Cincinnati reported on his experience using ultrasonic scanning to outline the carotid artery bifurcation. He indicated that in addition to stenotic lesions, large ulcers were usually easy to detect, but that very small ulcers cannot easily be seen with B-mode scans. He emphasized that the follow up value of these testing procedures was important in studying what happens to carotid arteries and relating the natural history of development of arterial disease to treatment and post-operative follow up.

CT Scans and Infarcts

Dr. William Kinkel of the University of Buffalo reported on the contributions of CT scanning to understanding stroke. Dr. Kinkel related the findings on CT scans to autopsy findings. He indicated that the CT scan was usually reliable in determining large cerebral infarcts, but was not effective in identifying small cerebral infarcts and brainstem infarcts. Of the 52 infarcts he studied at autopsy, 28 were found before death by the CT scan, giving a 54% correlation. The size of the infarct is the most important factor in the accuracy of their detection by the CT scan and the accuracy increases significantly with increasing size of the infarct. In acute cerebral infarcts studied from zero to 7 days after onset, the most striking findings were gray matter enhancement, which was believed to be caused by hypoxia and resulting hyperemia. During the subacute phase, 8 to 21 days, there was decreased attenuation of the brain substance and infarcted tissue, with edema causing the indistinct boundaries between normal and abnormal tissue with a mass effect often in evidence. In chronic infarcts studied 3 weeks after onset, there was decreased attenuation of the infarcted area, the distinct borders were still present but there was a heterogenous appearance in the infarcted area. In general, the infarcted area was smaller than seen originally.

Dr. J. Keith Campbell of the Mayo Clinic Medical School reported on the temporal profile of cerebral vascular disease as demonstrated by the CT scan. Of 257 patients 21 had transient ischemic attacks and in this group, either early or late scanning showed positive findings in only 14% of the patients. He concluded that CT scan for study of patients with transient ischemia was of marginal diagnostic value. The patients were divided into 2 groups: one had a scan within 24 hours of onset; the second group had a late scan 7 to 10 days after the first. Cerebral hemorrhage was diagnosed with 100% accuracy in the 20 patients who had it. Among the 201 patients who had an infarct, the scan done early was positive in 62%; when done later it was positive in 64%. In patients with cerebral infarction, there was a decrease in the density of the infarcted tissue in 62%; in 30% it was iso-dense and the density was increased in about 6% of the patients. In 164 patients, 76 infarcts were located supratentorially, in 80% they were in the cortex and mantle, 55 were in the basal ganglia, and in 54 patients the location was infratentorial. The more severe the clinical neurological defect, the more likely was the CT scan to be positive. In a series of patients who had heart disease and who were believed to have cerebral emboli, the early scans were positive in 50% of the patients; in later scans in 70%. A mass effect was seen in 46%. Concluding, Dr. Campbell expressed the thought that the most important use of the CT scan was the demonstration of cerebral hemorrhage and that, occasionally, a CT scan picked up other lesions, such as brain tumors and subdural hematomas, to explain the stroke.

Dr. Molinari asked Dr. Campbell whether multiple small cerebral infarcts went undetected. The speaker agreed that often they did.

Dr. Myron Ginsberg of Miami University School of Medicine pointed out that B-mode ultrasound scanning of the neck may show a carotid ulcer which does not appear on arteriography. Dr. Olinger commented that despite this unusual event, angiography is still the "gold standard" for detecting carotid lesions.

Rapid Scanning

Dr. Dieter Heis reported that by using rapid scanning techniques, one can distinguish between gray matter enhancement and increased perfusion. In those patients with stroke who had contrast enhancement with rapid scanning, a rapid transit of contrast media through the cortical gray matter can be seen, suggesting increased perfusion and later gray matter enhancement which suggests trapping of the contrast in tissue. Dr. Kinkel indicated that gray matter enhancement must be related to trapping of the contrast media in tissue because it persists beyond several complete cerebral blood flows. Dr. Ginsberg raised the question whether surgeons were now prepared to operate on carotid arteries on the basis of B-mode scanning. Dr. Olinger replied that most surgeons were not ready to substitute B-mode scanning for angiography in order to determine whether or not surgery should be performed.

Migraine

Dr. James Lance of Sydney, Australia, reviewed the current concepts of migraine covering the physiology, biochemistry and clinical manifestations of the problem. Dr. Lance indicated that he believed that migraine was much more widely the cause of headache than was generally accepted and that many of the headache syndromes which were encountered in clinical practice were based on changes in cerebral vasculature which were similar to those seen in classic
migraine. He reported that many of the headaches that patients experienced, classified as tension headache syndromes, were probably vascular in origin and that most of the headache problems could be explained by some alteration of the characteristic responses of extracranial and intracranial vasculature. He reviewed the classic symptomatology of migraine headache pointing out the relationship of vas constriction intracranially to the prodromal symptoms and vasodilatation extracranially as the cause of the head pain. He reviewed the connection between serotonin levels and migraine headache. However, he reported that he did not believe that the change in serotonin levels could explain all the features of migraine headache, including the unilaterality of the symptoms and the ability of the head pain to change rapidly from side to side.

Therapeutic approaches to the problem of migraine headache were discussed by Dr. Dewey Ziegler of the University of Kansas. He reviewed the use of various medications for the treatment of migraine headache, covering analgesic medication and indicating that most migraine headaches can be managed with simple analgesics such as aspirin. He added that physicians should be cautious with analgesics that might be addictive.

Dr. Ziegler reviewed the role of ergot preparations in the treatment of migraine, indicating they were most satisfactory when used at the start of the headache. But he added that there was still confusion about where these agents were best absorbed, and how effective they were. He discussed the use of anti-serotonin agents such as methysergide (Sansert), reporting that these agents are the most effective in preventing migraine headache. In his discussion of the pharmacological programs for breaking up the migraine cycle, he mentioned the use of agents such as ergotamine, dimethylsergide, amitryptyline, propranolol and aspirin. He gave the indications and the contraindications for each of these substances mentioning reports on the effectiveness of amitryptyline. He mentioned the use of bio-feedback techniques, indicating that the reports of good results are variable.

In the discussion, Dr. Meyer asked why migraine is hemi-cranial and Dr. Lance said that at this time the physiological and biochemical understanding of migraine headache did not provide a basis for this rather characteristic symptomatology of migraine.

Dr. Michael Welch of Houston commented that migraine is a female disease since it was most common in women. He mentioned a report indicating that there was occasionally some disturbance of fifth nerve innervation unilaterally in patients with migraine headache and reported that he had seen an individual with migraine headache who later developed a rash in the ophthalmic division of the trigeminal nerve on the headache side of the head, which was ultimately shown to be herpes simplex infection.

**Stroke Therapy**

The next session was devoted to a review of the scientific basis for therapy in stroke. Dr. Fred Plum of Cornell University Medical College reviewed present understanding of the role of ischemia, energy failure, age, hypercythemia, blood-brain barrier necrosis and low post-ischemic perfusion and its connection with the outcome of stroke. He reported that current experimental data indicate that an adverse outcome for stroke is caused by the amount of cerebral ischemia, the degree of energy failure in neural tissues, the presence or absence of hyperglycemia during the ischemia, the degree of decline of post-ischemic cerebral perfusion, the presence or absence of hypercythemia including red cells and platelets, the age of the patient, and the degree of blood-brain barrier necrosis. He believed that for a good outcome for a patient with stroke most of these abnormalities had to be completely reversed. In reviewing the problem, he noted that the experimental and clinical literature indicates that hypoxia is reasonably tolerated by the brain but that oligemia is not, and oxygen decrease must be accompanied by oligemia to produce major ischemic infarction. Acetylcholine synthesis has been shown to drop with levels of hypoxia which apparently cause no decrease in energy levels in cells. He reported that current studies of cerebral ischemia indicated that hyperglycemia and other metabolites associated with hyperglycemia cause more cerebral damage and may increase the fatality rate in patients with stroke. Studies clearly indicated that a high post-ischemic cerebral blood flow improved survival and that angionecrosis and blood-brain barrier breakdown caused by ischemia is a serious problem and is usually accompanied by an edema and fatality. Blood-brain barrier leakage in oligemic infarction is associated with increased pinocytosis which was known to occur during the first few minutes following ischemia with endothelial necrosis occurring later. In reviewing the experimental data on cerebral infarction from clinical studies, he noted that brain edema and brain necrosis began to be apparent in 2 or 3 hours after the ischemic insult. He pointed out that if there is no change in blood flow, in experimental studies, there was no blood-brain barrier damage, at least for 30 minutes after the onset of ischemia but that after 60 minutes of ischemia, there was some damage. He indicated that in clinical management of stroke, it was important to maintain perfusion pressure, control hemagglutination by some kind of a filtering process, halt blood-brain barrier injury, if possible, and hold neural injury to a minimum while preventing tissue acidosis.

**Barbiturate Therapy**

The usefulness of barbiturate therapy in stroke was discussed by Dr. Peter Safar of Pittsburgh University. He reported evidence that barbiturates protect against ischemic injury from both global and focal ischemia and said that Nembutal and Hexobarbital are protective if given before the ischemic insult or immediately after its occurrence. The problem in the use of these barbiturates is that cardiac depression and arrest have occurred with large doses of either substance. He indicated the need for a clinical study of the usefulness of barbiturate for the treatment of stroke,
and said that a randomized study treating global ischemia with barbiturate had been started in 10 institutions in 6 countries and that 40 patients have been admitted to this study for an initial trial of thiopental loading. To date, the results have been inconclusive. Initial reports indicated that 60% of the patients seemed to have recovered. He believed that an anesthetic dose of barbiturates was needed after cerebral infarction and cardiac arrest.

Dr. John Michenfelder of Mayo Clinic Medical School, continued discussion on “Unresolved Questions in Barbiturate Therapy.” He pointed out that results in animal experiments using barbiturate protection before, during, or after cerebral infarction were variable and that there were considerable differences of opinion about the usefulness of barbiturate protection against cerebral infarction. Studies have shown that during hypotension and ischemia ATP levels were preserved better in experimental situations when the thiopental was used. He reported on experiments with monkeys, indicating that those treated with pentobarbital before ischemia seemed to do better than those not so treated. He described the mouse survival experimental design in which mice or rats exposed to 5% inspired oxygen were observed until respiration ceased. He reported that there was clearly an increased survival among the mice treated with pentobarbital up to 6 milligrams per kilogram. He mentioned that the level of oxygen in these experiments was critical; mice survived well breathing oxygen at tensions of 6% and 5%, but most of them died at levels of 4% oxygen in inspired air. He believed that barbiturate decreased the cerebral metabolic rate for oxygen but this phenomenon is only of importance in functioning brain and he did not believe that the marked decreases in the cerebral metabolic rate for oxygen was the factor that made the difference in the survival of animals exposed to hypoxia. Further studies indicated that to be effective in the protection of cerebral ischemia, a barbiturate must have an anesthetic effect. Barbiturates have a variety of effects: they decrease the cerebral metabolic rate for oxygen during regional or global ischemia, and they reduce intracranial pressure in regional but not global ischemia. Dr. Michenfelder believed that the most likely explanation for the effect of barbiturate protection against cerebral ischemia was decreasing the cerebral metabolic rate for oxygen.

Dr. Nemoto of the University of Pittsburgh reported that giving barbiturates to animals exposed to experimental cerebral ischemia appeared to decrease the level of circulating free fatty acids.

Dr. Frank Yatsu indicated that he had treated 26 patients with stroke with barbiturates giving a low dose 60–100 mg 3 times a day for 2 days, 12–20 hours after the onset of stroke without producing any significant difference in the 2 groups in his randomized study. He reported that PGA₂ infusion to prevent an accumulation of platelets at the site of arterial injury had been tried but the results were not conclusive.

Dr. Hachinski, Sunnybrook Medical Center, Toronto, asked Dr. Plum about the role of hyperglycemia in the causation of more severe strokes. Dr. Plum indicated that his data did not clarify this issue as yet.

Dr. Millikan recalled that in a previous study of Dr. Lassen, one of the groups of patients was treated or narcotized with barbiturates for 72 hours following the acute onset of stroke. These patients received artificial ventilation but some spontaneously ventilated. Dr. Millikan asked about the outcome of this group of patients. Dr. Lassen reported that there was no difference between those patients who had been treated with barbiturates who were hypocarbic and normocarbic, while the patients who had spontaneous breathing appeared to do the best of all.

Dr. Plum reported that there is evidence that high-level intensive care can prolong life. In his studies of head injury comparing the outcome between the patients treated in the United States and the United Kingdom, there were strikingly different results, with a prolongation of life in the United States. He reported that in the United Kingdom, patients with severe head injury died in 2 to 3 days but in the United States they died in 5 to 7 days. He believed this was due largely to the level of acute care that was given rather than any fundamental change in the outcome of the situation.

Dr. David Levy of the Cornell Medical College indicated that in experimental stroke models, indomethacin and prostacyclin had been used to prevent platelet accumulation. This had occurred but he could not tell whether the effect was due to indomethacin or prostacyclin but he believed that the use of prostacyclin PGA₂ might be useful in preventing platelet accumulation.

Dr. Hachinski talked about the phenomenon of deterioration following acute cerebral infarction and raised the question of the relation of this change to cerebral edema. He mentioned that in this situation the CT scan is often negative, which did not support the notion of cerebral edema as a cause. In approximately 20% of the patients in his study, there were systemic complications, mainly cardiac, but also problems of renal and respiratory failure. These systemic complications were thought to be the cause of decline in patients after stroke, and this was substantiated in 23 of the 81 patients studied.

Dr. Simeone of the University of Pennsylvania asked if the use of barbiturates in head injury was still considered experimental and also whether it was believed to be an experimental form of therapy in acute stroke. There was no unanimity of opinion during the discussion that followed but the consensus appeared to be that both treatments were still experimental.

Parenchymal Hematoma

Dr. Robert M. Crowell of Massachusetts General Hospital presented his data on the “Surgical Treatment of Parenchymal Hematoma.” He noted that with the use of the CT scan it has been found that 14 to 16% of strokes are actually caused by intracerebral hemorrhages. He reported that there is some evidence
that there has been a decrease in the incidence of intra-cerebral hemorrhages with the use of antihypertensive treatment. In reviewing the problem of cerebral hematoma, he indicated that the most useful diagnostic tool has become the CT scan and that the angiogram is generally used only as a secondary aid, showing an occasional arteriovenous malformation, neoplasm or aneurysm. The initial treatment for patients with intracerebral hematoma is directed towards control of blood pressure and reduction of intracranial pressure with steroids or mannitol and a control of seizures with an appropriate anticonvulsant. Among his 26 patients, 17 had no evidence of increased blood pressure; 21 of the 26 patients with hemorrhage were alive and 17 had a good outcome. Only 20 were treated surgically; of these 14 were alive, and 13 were improved. In general, he found that the alert, awake patient did well with surgery and those who were in coma when they came to surgery did poorly. His general indications for operation were the demonstration of a lobar hematoma with clinical deterioration or evidence of a cerebellar hematoma.

Dr. James T. Robertson of the University of Tennessee Medical College reviewed the usefulness of carotid endarterectomy before, with, or after coronary bypass surgery. The issue in this problem is that frequently patients who have had coronary bypass operations develop stroke and that a frequent cause of morbidity and mortality in individuals undergoing carotid endarterectomy is myocardial infarction. He believed, from his studies, that prophylactic coronary endarterectomy was not greatly useful for patients undergoing carotid endarterectomy but if disease of both systems was advanced, there was some advantage in simultaneous coronary and carotid endarterectomy. With the combined operation, there seemed to be a slightly increased chance of having a stroke but that the stroke rate was not increased when the 2 operative procedures were staged.

Dr. H. J. M. Barnett, of the University of Western Ontario, reviewed the current status of EC/IC bypass study, and reported that 64 centers are now involved in this research project and that about 620 patients have been entered into the data bank. Of these patients 350 are from North America, 185 are from Europe and about 50 from Japan. Dr. Barnett concluded that by 1984 there will be enough patients in the study and adequate follow up to allow analysis.

Dr. James Halsey of the University of Alabama, Birmingham, indicated that his studies of cerebral blood flow following carotid endarterectomy indicated that there was not much increase in flow immediately following operation in the hemisphere supplied by the particular artery, but a month later the flow has increased back up to the level of the nonoperated side.

Dr. Brust of Harlem Hospital in New York City asked Dr. Robertson if he favored surgery for asymptomatic bruits. Dr. Robertson replied that he believed that surgery was not indicated for patients with asymptomatic bruits.

Dr. Nicholas Zervas of the Massachusetts General Hospital commented on cerebral vasospasm, indicating that it is reported most often in patients with large amounts of blood in the subarachnoid space. But some patients with large amounts of blood do not have spasm and often patients with very small amounts of blood had a great deal of spasm. He concluded that not all cerebral vessels act in the same way.

Dr. Barnett asked whether or not bypass pumping required for coronary artery bypass surgery could cause cerebral problems or is it the carotid artery that causes the cerebral problems. Dr. Robertson replied that it was not necessarily always carotid artery disease that caused cerebral troubles and, in fact, a number of cerebral problems following myocardial revascularization are not necessarily related to carotid artery disease.

Dr. Wolfe of Boston University School of Medicine indicated that the Framingham Study had reviewed the status of 170 patients who had stroke. Among this group some had asymptomatic bruits. In this group less than one-third had the stroke on the side of the bruit. Of the 170 patients, 50 died with myocardial infarction and stroke; 21 died with only myocardial infarction.

Dr. Robert Ackerman reported on a group of patients with asymptomatic bruits who were studied in the non-invasive cerebrovascular disease evaluation laboratory. He indicated that these individuals have arterial stenosis but most of them do not seem to progress, and during his follow up study they have not had strokes.

Hematologic Studies

The last session of the meeting was on "Hematologic Studies in Stroke." Dr. David Levy of the Cornell University Medical College reported for Dr. Babette Weksler. She discussed the basic mechanisms and recent advances in the hematologic studies in stroke, reviewing platelet aggregability and adhesion to a damaged endothelium. She reported on 82 patients with TIA, one half of whom had increased platelet aggregation during the first 10 days following onset of TIA. She reported that in thrombocytosis and thrombocythemia there was increased platelet aggregability. The relationship of arachidonic acid to cyclooxygenase, PGE2 and thromboxane A2 were discussed, emphasizing that the exposure of collagen in the vessel wall to the circulating blood stream is an important factor in causing platelet adhesiveness. Aspirin inactivates the cyclo-oxygenase system but does not appear to inhibit adhesion of the platelet to the vascular wall. It was suggested that indomethacin plus PGI2 would probably be a good combination for inhibiting platelet adhesions to a damaged vascular wall.

Dr. Kenneth K. Wu of the Rush-Presbyterian-St. Luke's Medical Center in Chicago reviewed "Labeled Platelets and Fibrinogen in Stroke." He mentioned that the major problem in all of these studies of thrombotic activity is that such activity cannot be directly assessed in a patient. He described
radionuclide labelling of platelets, mentioning that the use of Indium III labelled platelets was the most effective way of studying platelet activity as the half-life of the labelled platelets was 2.8 days and only a small amount of blood is necessary for labelling. The radioactivity of Indium III is good for imaging and survival studies. He noted that it was possible to image vascular lesions and to measure the survival time of platelets with this method but that the problems were sensitivity and specificity. He reported one study which correlated carotid angiography with platelet imaging in 34 patients. It was found that the sensitivity of the method was 35% and the specificity was about 86%. The problem with platelet studies is the uncertainty of the meaning of the findings: whether they mean acute injury to the vessel wall, passive adherence, or trapping of labelled platelets on atherosclerotic plaques or plugs.

**Blood Viscosity and Stroke**

Dr. David J. Thomas of St. Mary's Hospital Medical School in London reviewed the relation of "Blood Viscosity and Stroke." He reported that what he believed to be blood viscosity rises with the hematocrit, and that viscosity of blood almost doubles when the hematocrit goes from 40 to 50. He believed it was not dangerous to decrease the hematocrit in the patients with stroke as this often reduced blood viscosity and improved the cerebral blood flow. In a study of the level of alertness in patients with a high hematocrit, Dr. Thomas noted that when the hematocrit was lowered, patients became more alert. He reported a lower incidence of stroke in patients with low hemoglobin values as found in the Framingham study in 1972 and a Japanese study showing a greater danger of stroke with a high hematocrit.

Dr. Anthony Fletcher of Washington University in St. Louis discussed fibrinogen and cell interactions in patients with stroke. He reported that he found high molecular weight fibrinogen complexes were more frequent in patients with stroke and particularly more frequent in patients with severe stroke.

Dr. Thomas reported he believed that a high hematocrit might increase blood pressure but he was not clear how this might happen. He believed that the optimum hematocrit for oxygen delivery is 35 to 40%.

**ANNEX**

**PARTICIPANTS IN THE 12TH RESEARCH CONFERENCE ON CEREBROVASCULAR DISEASE**

Robert H. Ackerman, M.D.
Director, Cerebral Blood Flow and Carotid Evaluation Laboratories
Massachusetts General Hospital
Boston, MA 02114

Nathaniel Alpert, Ph.D.
Applied Physicist
Massachusetts General Hospital
Boston, MA 02114

H.J.M. Barnett, M.D., F.R.C.P. (C), F.A.C.P.
Professor and Chairman
Department of Clinical Neurological Sciences
The University of Western Ontario
London, Ontario, Canada N6A 5A5

Jean D. Benedict, M.D.
Health Scientist Administrator
Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health
Bethesda, MD 20205

Robert W. Brennan, M.D.
Professor of Medicine (Neurology)
The Milton S. Hershey Medical Center of the Pennsylvania State University
Hershey, PA 17033

John C.M. Brust, M.D.
Associate Professor of Clinical Neurology
Columbia University College of Physicians and Surgeons
Harlem Hospital Center
New York, NY 10037

J. Keith Campbell, M.D.
Associate Professor of Neurology
Mayo Medical School and Mayo Clinic
Rochester, MN 55901

John J. Caronna, M.D.
Associate Professor of Neurology
University of California, San Francisco
San Francisco, CA 94110

Jorge Cervos-Navarro, Prof., Dr.Med.
Geschäftsf. Direktor
Institut für Neuropathologie, Klinikum Steglitz, Free University Berlin
Berlin (FRG)

John Correia, Ph.D.
Assistant Professor of Radiology
Harvard Medical School — MGH
Boston, MA 02114

Robert M. Crowell, M.D.
Neurosurgeon
Massachusetts General Hospital
Boston, MA 02114

J. Donald Easton, M.D.
Professor and Chairman
Department of Neurology
University of Missouri Medical Center
Columbia, MO 65212

James O. Eichling
Associate Professor of Radiology
Washington University School of Medicine
St. Louis, MO 63110

Benjamin H. Eidelman, M.D.
Assistant Professor
Department of Neurology
University of Pittsburgh
Pittsburgh, PA 15261

Tibor Farkas, M.D.
Senior Scientist
New York University Medical Center
Department of Psychiatry
Division of Neuropsychopharmacology
550 First Avenue
New York, NY 10016

William Feddel, M.D.
Montreal Neurological Institute
Department of Neurology and Neurosurgery
McGill University
Montreal Neurological Hospital
3801 University Street
Montreal, Quebec H3A 2B4, Canada

Professor Cesare Fieschi
3a Cattedra di Clinica Neurologica
University of Rome
00185 Rome, Italy

C. Miller Fisher, M.D.
Professor of Neurology
Harvard Medical School
Boston, MA 02114

Anthony P. Fletcher, M.D.
Associate Professor of Medicine
Washington University School of Medicine
Veterans Administration Medical Center
113 Jefferson Barracks
St. Louis, MO 63125
A. L. Sahs, M.D.
Professor Emeritus
University of Iowa
Iowa City, IA 52242

Barton A. Sandok, M.D.
Associate Professor of Neurology
Mayo Medical School
Rochester, MN 55901

Peritz Scheinberg, M.D.
Professor and Chairman
Department of Neurology
University of Miami School of Medicine
Miami, FL 33101

Bruce S. Schoenberg, M.D., M.P.H.
Head, Section on Epidemiology
National Institute of Neurological and Communicative Disorders and Stroke
Bethesda, MD 20892

Robert G. Siekert, M.D.
Professor of Neurology
Mayo Medical School
Rochester, MN 55901

Frederick A. Simeone, M.D.
Associate Professor of Neurosurgery
University of Pennsylvania School of Medicine
Philadelphia, PA 19104

Lindsay Symon, TD, FRCS
Professor of Neurological Surgery
Institute of Neurology, University of London
The National Hospital, Queen Square
London WC1N 3BG England

Juan M. Taveras, M.D.
Radiologist-in-Chief
Massachusetts General Hospital
Professor of Radiology
Harvard Medical School
Boston, MA 02114

Michel M. Ter-Pogossian, Ph.D.
Professor of Radiation Sciences
Washington University School of Medicine
Malinckrodt Institute of Radiology
510 South Kingshighway
St. Louis, MO 63110

David J. Thomas, M.D.
Consultant Neurologist
St. Mary's Hospital Medical School
London W2 1NY England

C. J. Thompson
Systems Engineer
Montreal Neurological Institute
3801 University Street
Montreal, Quebec H3A 2B4, Canada

James F. Toole, M.D.
Professor of Neurology
Bowman Gray School of Medicine
Winston Salem, NC 27103

Michael D. Walker, M.D.
Acting Director, Stroke and Trauma Program
National Institute of Health, NINCDS
Federal Building, Room 8A08
Bethesda, MD 20892

Arthur G. Waltz, M.D.
Chairman, Department of Neurology
San Francisco, CA 94120

K.M.A. Welch
Associate Professor of Neurology
Baylor College of Medicine
Houston, TX 77030

Jack P. Whisnant, M.D.
Professor and Chairman
Department of Neurology
Mayo Clinic and Mayo Medical School
Rochester, MN 55901

Philip A. Wolf, M.D.
Professor of Neurology
Boston University School of Medicine
80 E. Concord Street
Boston, Massachusetts 02116

Kenneth K. Wu, M.D.
Associate Professor of Medicine and Chief, Coagulation and Thrombosis Unit
Rush-Presbyterian-St. Luke’s Medical Center
173 W. Congress PKWY
Chicago, IL 60612

Dr. Lucas V. Yamamoto
Associate Professor Neurology & Neurosurgery
Director, Neuroradiology Laboratory
McGill University
Montreal Neurological Institute
3801 University St.
Montreal, Quebec H3A 2B4, Canada

Frank Yatsu, M.D.
Professor and Chairman
Department of Neurology
University of Oregon School of Medicine
Portland, OR 97201

Nicholas T. Zervas, M.D.
Chief, Neuroradiology Service
Massachusetts General Hospital
Professor of Surgery
Harvard Medical School
Boston, MA 02114

Dewey K. Ziegler, M.D.
Professor and Chairman
Department of Neurology
Kansas University Medical Center
Kansas City, KS 66103
F H McDowell and C H Millikan

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