Summary of 11th Princeton Conference on Cerebrovascular Disease

Nassau Inn, Princeton, NJ, March 5–7, 1978

FLETCHER H. MCDOWELL, M.D. AND CLARK H. MILLIKAN, M.D.

A REVIEW of the currently available animal models for cerebral ischemia and stroke was the first topic of the conference. Dr. Erland Nelson, Chairman of the Conference, mentioned that Cooper in England in 1836 had tied an animal’s carotid arteries to find what happened and therefore should be given credit for establishing the first stroke model. An animal model for stroke should have the following characteristics: sudden onset, progression and regression of symptoms as seen in humans, be economical and usable prospectively. In the human, stroke is associated with many variables, including age, atherosclerosis, and high blood pressure and some of these variables can be reproduced in animals, many cannot.

Dr. Gaetano Molinari reviewed the history of stroke models and mentioned that the ideal model should resemble, as closely as possible, the clinical picture seen in humans with cerebrovascular accidents. Most stroke models used healthy young animals but stroke in humans largely occurs in elderly individuals. In older experimental animals, especially older gerbils and possibly the stroke-prone hypertensive rat, there may be a higher incidence of stroke. Aged animals apparently have less elasticity in their cerebral vessels and higher cerebrovascular resistance. Dr. Molinari concluded that no current animal model for stroke perfectly mimicked the human situation. In the usual models, cerebral ischemia is produced by a variety of means including embolization, hypotension, either by reducing general blood pressure or occluding all neck vessels to the head, and by individual cerebral vessel occlusion. In most experimental animals, vessel occlusion produces highly variable results depending on the animal. Many of the animals have wide variations in cerebral collateral circulation. Dr. Molinari expressed belief that clot emboli perhaps have the advantage in producing cerebral infarction as they do not require invasive procedures; their disadvantage is that they are unpredictable in the amount and site of cerebral infarction produced.

Duty of Pathologist

Dr. John Moossy reviewed the role of the morphological pathologist in the production of experimental stroke and indicated that it was the duty of the pathologist to validate the results of experimental stroke in each model, using all the facilities available including macroscopic, microscopic and electron microscopic examination. He said the electron microscope is best for the early detection of cerebral ischemia as it can distinguish reversible from irreversi-
ble neuronal damage. He pointed out that no experimental model exactly duplicates the infarction found in humans as a result of cerebral atherosclerosis. Total cerebral ischemia, used by some investigators, unfortunately produces multifocal, bilateral, and unpredictable amounts of cerebral ischemia. Cerebral emboli, which occlude the main stem of the middle cerebral artery, produce the best and most consistent results and require less trauma. Dr. Moossy agreed that autologous clot emboli best produced cerebral pathology with infarctions similar to that in humans, but the embolic method is irreversible. Intermittent occlusion of specific vessels can produce ischemia which can be reversed. Global cerebral ischemia, as produced in animals, has very little relevance to humans following cardiac arrest, which produces global cerebral ischemia. There are so many systemic problems with global cerebral ischemia that the animals rarely survive. Dr. Moossy suggested that Old World primates are the best experimental animals but stroke prone animals, especially stroke-prone hypertensive rats, may become excellent models.

Dr. Arthur G. Waltz discussed the physiology of cerebral ischemia and infarction in animal models. The amount of paresis seen in the experimental animal was usually less than in humans and other deficits, such as depression in levels of consciousness and seizures, were common. Neurologic deficits were difficult to determine in small animals. In the pathophysiology of the cat with occlusion of the middle cerebral artery one finds large infarctions involving the caudate nucleus associated with a reduced cerebral blood flow. Dr. Waltz said that cerebral blood flow to produce ischemia must drop to 20 ml/100 gm/min of blood in tissue and irreversible changes occur if this drops to 12 ml/min.

Following ischemia, there is usually a period of hyperemia associated with cerebral edema. Dr. Waltz said that periods of decline in cerebral blood flow following experimental ischemia may be unpredictable and blood flow may remain decreased for a long time. Middle cerebral artery occlusion frequently produces bilateral changes in cerebral blood flow but more marked changes on the occluded side. It was pointed out that an ideal experimental model should allow for instantaneous stopping of metabolism if more than cerebral blood flow is to be studied. This would allow metabolic changes in neurons to be evaluated.

Dr. Robert Crowell mentioned that he had developed a model which allowed for reversible cerebral ischemia and measurement of blood flow in an awake animal. The animal could be neurologically evaluated frequently.

Under-perfused Neurons

Dr. William Oldendorf suggested that a model should be developed to study neurons which were under-perfused and which had some potential for restoration of function if perfusion returned to normal. He added that an animal which had suffered cerebral infarction did not lead to an understanding of how to correct cerebral ischemia in humans. He suggested that an animal model using increased intracranial pressure to reduce cerebral blood flow should be considered as it can produce hypoperfused areas with restoration of blood flow.

Dr. Konstantin-Alexander Hossman reported that he had increased intracranial pressure to produce ischemia but flow decrease was not uniform nor homogenous. He found that in this model the period of reversible ischemia was lower in awake animals than those anesthetized. Dr. Hossman indicated that it was important to study mitochondrial changes in neurons because they might provide a common link between experimental animals and the humans.

Brain Biochemistry, Stroke Dynamics

The second section of the meeting was devoted to in vivo mapping of human brain biochemistry and hemodynamics in stroke, moderator Dr. Marcus Raichle.

Dr. Raichle reviewed available techniques for mapping human brain biochemistry. He reported on the use of isotopic agents, such as 15O, to determine regional cerebral metabolic rate for oxygen and measuring cerebral blood flow, and the use of 2-deoxyglucose to study the regional metabolism of the glucose in the brain. He also reviewed the use of 133Xenon inhalation and tagged radioactive albumin for studying regional blood flow by autoradiography. He pointed out that the developments in the field of emission tomography, using substances such as 18O and 2-deoxyglucose were improving the study of regional brain metabolism in vivo.

Dr. John Eichling discussed noninvasive tracer techniques for determining cerebral blood flow including 133Xe, stable xenon, 57Cr and 17O and talked of some of the problems with each of these methods. The 133Xe wash-out technique is highly dependent on the partition coefficient for xenon which has a high lipid solubility and a low energy emission. The method is greatly affected by the hematocrit in large and small vessels. Local lipid content of tissue is highly variable. With xenon there is a considerable tissue attenuation of the radioactivity and interference with measurements of radioactivity from superficial tissues. With 133Xe there is heavy attenuation of x-ray radiation and a high scatter and an extremely high noise level in the data. The method does not recognize nonperfused tissues and is best used for documenting areas of high flow.

Dr. Eichling commented that the stable xenon method produces excellent spatial resolution and uncertainty about the partition coefficient of xenon is minimized. The disadvantages are that the equilibrium time is long, (up to 45 min) especially for low flow areas; there is trouble monitoring the fast component because the lipid content of gray matter is low so the accuracy of blood flow determination is less; the noise level; the absorbed radiation dose is high, and the method is expensive. The stable 57Cr method has the same problems as the xenon method.
In reviewing \(^{18}O\) labeling, he mentioned that the disadvantages are that the partition coefficient is uncertain, that the computed regional cerebral blood flow is subject to large errors, that it is potentially most accurate in areas of high flow, and is expensive.

Enhancement Techniques

Dr. George H. du Boulay reported on use of transmission tomography with enhancement techniques using either contrast media with iodine or other agents such as xenon by inhalation. Using contrast enhancement markedly improves the diagnostic abilities of transmission tomography. With xenon enhancement, there is a change in attenuation values which is most marked in the white matter, less in the gray matter, making it difficult to distinguish between them. Xenon techniques with enhancement are of value but the system depends on accurately subtracting one identical cut from another and making identical cuts is difficult. Xenon enhancement is useful in showing the demarcation of infarcted tissue.

Dr. Michel M. Ter-Pogossian described use of emission tomography in which a radioactive molecule is administered and the emitted radioactivity measured. He pointed out that for transmission tomography to increase in accuracy it requires concentrations of high atomic weight elements, whereas emission tomography requires only small amounts of substances which have physiological function, such as oxygen, carbon, nitrogen, or fluoride. The weakness of the emission system is that it requires a cyclotron to make these elements radioactive, and all the substances used have a short half-life. A large number of labeled pharmaceuticals are now available for emission tomography including ammonia, glutamine, alcohol, fatty acids, and steroids. The system requires a large amount of equipment but much of it is almost identical to that needed for transmission tomography. Emission tomography is being used with radioactive sodium which indicates areas of perfusion, radioactive hemoglobin which gives brain volume, radioactive EDTA which indicates the stability of the blood-brain barrier and radioactive glucose which gives some indication of glucose metabolism.

Dr. Walter Obrist pointed out that the main problem with these methods was often extracerebral contamination and recirculation problems. Dr. John A. Correia said that emission scans using a positron carrier had advantages and a continuous input of the positron substance, such as oxygen and carbon dioxide, was possible. He also indicated that cylindrical volumes of brain tissue were studied but there was a high percentage of error with higher flows. Dr. Sadek Hilal commented that error decreased with a count increase and errors would continue to decrease with better equipment using a mass-spectrophotometer.

Emission CT

Dr. Marcus E. Raichle noted that emission computerized tomography can measure blood volume, blood flow and brain metabolism. With this method it is possible to determine regional cerebral blood flow and detect differences in flow between the right and left side of the brain in right and left handed people. Carbon-labeled monooxyhemoglobin is helpful in detecting changes in blood volume. The carbon is tagged to the hemoglobin molecule and, as the red cells circulate only in the intravascular compartment, this gives a good estimate of blood volume. Regional metabolic activities can be measured by using carbon 11-labeled glucose and 18-fluoride deoxyglucose. He pointed out the advantages of using substances such as carbon 11-labeled glucose which is metabolized and leaves the cell as well as 18-fluoride deoxyglucose which enters the cell, is phosphorylated, and cannot leave neurons because the brain cannot metabolize it. Thus brain levels remain constant over long periods of time. With such substances it is possible to study the entry of agents into brain cells, their metabolism while in the cell and their exit time. Tracers such as carbon-labeled glucose are biologic, safe and nontoxic. Their disadvantage is that they have low radiation output and a short period of measurement. Fortunately, these measurements are easily repeatable. The problem with emission tomography is that the resolution powers are quantitatively smaller than for other methods. Using emission tomography, the metabolism of a large number of substances can be studied — carbon dioxide, ammonia, glutamine, glutamic acid, alcohol, fatty acids, and steroids. It is also possible to measure neurotransmitters and receptors and study the distribution and activity of neurotransmitters such as dopamine, glycine and norepinephrine. It is also possible to study platelet receptors. Dr. Raichle demonstrated a study in which the platelets had been radioactively labeled and their distribution observed. Platelets labeled with indium can be shown to accumulate in vessels at the sites of injury or atherosclerosis.

Dr. David E. Kuhl reported on emission tomography in the study of brain metabolism during seizures showing increased blood flow and metabolism at seizure sites.

Dr. William H. Oldendorf questioned the cost of xenon inhalation cerebral blood flow measurements. Dr. du Boulay mentioned that in England it was possible to reduce the cost of xenon to approximately $120 to $160 per examination; in the United States it was $300 to $400.

Dr. Alan Lockwood cautioned against use of radioactive ammonia in determining brain metabolism. He indicated that radioactive ammonia is incorporated into glutamine in the brain, and the ammonia is trapped. In patients with liver failure, where there is high ammonia level in the central nervous system, false notions arise about what is occurring in the brain.

Infrared Monitoring of Cerebral \(O_2\)

Dr. Frans Jöbsis discussed infrared monitoring of cerebral oxygen using spectrophotometry. Functions of the Krebs cycle can be evaluated using this technique by focusing a near infrared range light source on...
Brain Edema After Infarction

The third session of the conference was devoted to brain edema following brain infarction. Moderator Dr. Julio Garcia said that after arterial occlusion, fluid content of the tissue increased with swelling of astrocytes around capillaries. Edema begins almost immediately after infarction; it is not present with total ischemia but is more likely with partial ischemia.

Dr. Hanna Pappius traced the evolution of edema following experimental infarction using middle cerebral artery occlusion in the dog, cat and gerbil. She noted that after 1 hour there was a decrease in the dry weight of tissue, and increase in the cellular content of sodium, and a decrease in the content of potassium. She said that the opening of the blood-brain barrier, allowing changes in the potassium and sodium content of tissue, occurs between 1 and 8 hours after onset of infarction. She also pointed out that the changes may be reversible, particularly on the infarct periphery.

Dr. K.-A. Hossmann reviewed his experience with changes in brain water following middle cerebral artery occlusion in cats. He noted that with ischemia all frequencies of the EEG dropped on the occluded side. There was a decrease in cerebral blood flow and a change in the sodium-potassium ratio in the tissue with an increase of sodium and a decrease of potassium. He postulated that edema following infarction was due to decreased function of the ion pump. He reported that there was evidence that vasogenic edema, in which there is a breakdown of blood-brain barrier, is different from edema found with infarction.

Steroids

Dr. Robert Katzman reviewed the history of treatment of edema following cerebral infarction, indicating the large number of agents which had been tried, including anti-inflammatory and hyperosmolar agents which dehydrate the brain. What evidence there was for successful treatment of cerebral edema seemed to be connected with the use of steroids. Steroids decreased the spread of edema, possibly decreased the production of cerebral spinal fluid, and increased the resolution of edema. Hyperosmolar
agents were known not to affect cerebral edema but did dehydrate normal brain giving added space for the edematous brain. All the reports of efficacy of dexamethasone (Decadron) following cerebral infarction indicated that it had some use. Steroids must be used in very large doses similar to the size of the dose following head injury. It may be necessary to give loading doses of Decadron as high as 80 to 100 mg with high maintenance doses thereafter. He also said that current methods of evaluating improvement following stroke may be too insensitive to demonstrate an effect of Decadron in edema. Agents such as glycerol, furosemide (Lasix), and dextran had been used in the treatment of edema but no long-term difference in patients has been evident.

Dr. George du Boulay pointed out that when edema is observed in the CAT scan it is usually associated with increased water content of tissue and a decreased cerebral blood flow. CAT scan evidence of a shift of brain substance was needed to indicate the presence of swollen hemispheres.

Dr. K. Zulch showed sections of brains with infarcts with edema and shift indicating the conspicuous effects of brain swelling and herniation following edema and its disastrous effects on the brainstem.

In a discussion on protecting the stroke patient from cerebral edema, Dr. Bruce cited a recent experience in San Diego where 5 patients received high doses of barbiturates in an attempt to protect the infarcted brain from ischemia and the effects of edema, but all the patients died.

Canadian Study

The fourth session of the conference was devoted to transient ischemic attacks and platelet adherence suppression with Dr. John Kurtzke as moderator. The Canadian study of the use of platelet suppressive drugs in transient cerebral ischemia was reported by Dr. H.J.M. Barnett. Prior to the Canadian study it was estimated that approximately 540 patients would be needed to prove or disprove that aspirin or sulfinpyrazone had definite effect in suppressing transient ischemic attacks and preventing future stroke. The study initially reviewed over 1,000 patients, 756 of whom were excluded, and 585 accepted. Patients were excluded because: a diagnosis of cerebral embolization from the heart; evidence that the cause of the transient ischemic attacks was hemodynamic with a major arterial stenosis; illness which would prevent the patient from completing the trial; and patient unwillingness to complete the trial. There were 307 patients excluded because their physician decided against admission. The 585 patients who were accepted for study were treated in 4 different ways. One group was treated with placebo alone, one with aspirin alone, and one with aspirin and sulfinpyrazone (Anturane) and one with sulfinpyrazone alone. Eight hundred mg of sulfinpyrazone and 1300 mg of aspirin were given daily. (Patients were not included in the study who had taken large amounts of these drugs within 3 months before the study). Angiograms were encouraged but not demanded. Of the studied patients 76% had cerebral angiograms, 82% of these were abnormal and 43% showed lesions in arteries appropriate to the symptoms. Complications from taking aspirin and sulfinpyrazone were low but included bleeding which was lowest in the aspirin treated group. The average follow up was 715 days or 26 months with a maximum duration follow up of 1,087 days. The end points of the study were continued transient ischemic attacks, stroke or death. Combined end points were reduced 19% in patients who took aspirin, but there was no evident reduction in patients who took sulfinpyrazone, or placebo. When stroke death alone was considered, there was a 30% reduction of stroke death risk in patients who took aspirin and no evident effect noted for sulfinpyrazone. When the study was analyzed for male/female differences there was a marked difference in that the benefits of taking aspirin in preventing TIA and stroke were largely confined to men. Among the men there was a 48% drop in transient ischemic attacks, stroke or death when aspirin was taken but none in women.

Questions Raised

The study was reviewed by Dr. Abraham Lilienfeld who raised a number of questions about the study including the degree of blindness, and the relative hardness of the end points. He pointed out that risk factors were unevenly distributed in the group studied. He also noted that some of the end point events were included which occurred 6 months after withdrawal from treatment. He was not convinced by the data presented that any of the drugs used were particularly effective. He commented on the United States trial conducted by Dr. William Fields and noted that in this study only transient ischemic attacks were influenced by taking aspirin, especially only patients who had multiple transient ischemic attacks seemed to have benefited from taking aspirin. The transient ischemic attack was a rather soft end point and frequently not a definite enough clinical event to make the end point certain. He said that from the United States study it was very difficult to say that aspirin was effective at all.

Dr. John Kurtzke said that in the Canadian study both aspirin and sulfinpyrazone seemed to be effective. He believed that the study should review the effects of sulfinpyrazone; a multiple drug effect might be evident.

Dr. James Robertson reported on a controlled trial of sulfinpyrazone on a small number of patients at the University of Tennessee. He said that he found a reduction in transient ischemic attacks and fatal completed strokes, and also in nonfatal myocardial infarctions in the sulfinpyrazone treated patients when compared to control.

Dr. David Sackett, who had done the statistical analysis of the Canadian study, replied to some of Dr. Lilienfeld's comments. The only individual who knew the allocation of patients to a treatment was the computer programmer. He said he believed that the end
points of stroke, stroke death and TIA were reasonably clearly defined and were effective as end points. The group had analyzed the apparent uneven distribution of risk factors and felt that they had not greatly influenced the study. He defended the inclusion of end results 6 months after withdrawal from aspirin on the basis that the effect of aspirin might last longer than the immediate period of treatment. Because of this the group believed it should extend the period of end point inclusion beyond the time period during which the patient took aspirin.

Dr. Clark Millikan asked where this study left the practicing physician in deciding whether or not to treat patients with aspirin. He pointed out that about half the U.S. stroke patients are women, which reduced the number of patients who could be effectively treated with aspirin by 50%. He noted that in an earlier report on the Canadian study, given in New Orleans, that treatment did not appear to be effective in patients with hypertension, which further reduced the number of patients who could be viewed as candidates for aspirin therapy. Dr. Millikan said he was alarmed by the reports of the statisticians at this conference that there may be no evidence of effect of treatment in these studies. He also remarked there was already wide publicity about the effectiveness of aspirin based on the American and Canadian studies. He believed future reports should be cautious about recommending aspirin as a definitive preventive treatment for stroke based on the current evidence, and that is should not be recommended as an absolutely curative measure for transient ischemic attacks or the prevention of stroke.

Cerebral Vasospasm

At the fifth session the moderator, Dr. Nicholas Zervas, reviewed cerebral vasospasm and pointed out that it was most definite after subarachnoid hemorrhage and produced a delayed ischemic effect in from 34% to 48% of patients. He said the delayed ischemic effect was due to marked vasoconstriction. Current concepts of the cause of vasospasm included serotonin, thromboxanes, prostaglandins, iron pigments and other vasoactive substances.

Dr. Andrew Somlyo discussed the mechanisms and some of the chemistry of vascular smooth muscle contraction. Smooth muscle contraction occurred in response to a large number of different stimuli in individual vascular beds in the brain. The action potential produced by smooth muscle was probably due to a sodium current, however he indicated that some smooth muscle does not generate action potentials during contraction and that these cells have been shown to have a greater depolarization associated with increased contraction under the effects of epinephrine. He outlined the gradation of electrochemical responses in the portal anterior mesenteric vein of the rabbit in response to increasing concentrations of epinephrine. Epinephrine causes a dropout of action potentials and eventually depolarization of the smooth muscle cell with sustained muscle contraction. He said that in triggering the contraction of smooth muscle changes in membrane potential did not exactly parallel the quantity of contraction. Electrical activation of smooth muscle cells is not the sole means of causing contraction and humoral agents may be effective as an additional mechanism.

Of significant interest is calcium which appears to activate contraction. In the absence of calcium, contraction does not take place to the same degree. The absence of calcium in fluid bathing smooth muscle leads to no or limited contraction. He pointed out there is, however, some calcium stored in smooth muscle which accounts for the slight contraction observed in calcium-free baths. He described the cytoplasmic reticulum, which has been demonstrated to be a calcium storage site, and noted that the cytoplasmic reticulum is near the cell surface and in contact with the extracellular space. There were a number of drugs which acted directly on the cytoplasmic reticulum to release calcium and institute smooth muscle contraction. Mitochondria did not seem to play a role in calcium storage.

Dr. Otis Blaumanis reviewed the hemodynamics and morphological aspects of vasospasm and raised the issue of whether it was bad and, if so, why. Did vasospasm cause significant blood flow resistance? In a smooth muscle-lined tube flow was equal at both ends — the small end as well as the large — and that the simple increase in blood flow velocity accounts for the equality of flow. Increased velocity of flow often produced shear stress which is most important at the endothelial wall of the artery. Frequently shear stresses are strong enough to tear the endothelium lining the vessel. Following stripping of the endothelium at sites of increased shear stress, there is marked platelet aggregation and thrombosis. The ultimate effect on flow changes depends on the degree of vessel narrowing.

Innervation and Receptor Sites

Dr. Christer Owman discussed the innervation and receptor sites of intracranial vessels and the relation of neural innervation of cerebral blood vessels to spasm. The cause of vasoconstriction in the vessels supplying the human brain is both neurogenic and metabolic. Cerebral vessels can respond to a large number of substances including dopamine, serotonin, norepinephrine, acetylcholine, vasoactive peptides and mast cells containing histamine. Cerebral blood vessels have an extensive norepinephrine innervation and post-ganglionic denervation causes a marked decrease in the norepinephrine seen in the tissue. He also noted from his studies that there is a marked variation in the amount of adrenergic innervation of blood vessels in the brain. It was highest in the cortex and lowest in those parts of the brain supplied by the verteobasilar artery. He cited experiments in which blood was introduced into the subarachnoid space, and the degree of fluorescence produced by the presence of adrenergic innervation decreased. The number of fluorescent nerves seen in and around the basilar artery was markedly reduced following subarachnoid hemorrhage. There was a maximum decrease in
noradrenergic concentrations in nerves around vessels about 3 days after bleeding. The adrenergic concentration stayed down for about 7 to 10 days. He said he believed that the cause of the drop of norepinephrine in nerve terminals was a failure of the re-uptake mechanism which was reduced for several days. This change caused an increased sensitivity similar to denervation super-sensitivity. In this setting the vessel becomes more sensitive to circulating norepinephrine and also to other vasoactive substances, such as serotonin, which might account for vasospasm.

Dr. George Allen pointed out that a number of drugs were available which experimentally blocked basilar artery contraction following subarachnoid hemorrhage. The rare earth element lanthanum blocks the influx of extracellular calcium and also reduces the concentrations of 5-hydroxytryptophane. He also mentioned that nephetamine and phenylephrine block the effect of extracellular calcium and the replenishment of intracellular calcium. Both of these agents effectively block constriction of the basilar artery as seen on an angiogram following subarachnoid hemorrhage.

Dr. John Bevan discussed some of the physiological phenomena associated with vasospasm. During spasm there is an increased responsiveness to histamine stimulation acting on smooth muscle cells to produce constriction. Contracture, a sustained contraction of a large vessel, developed in smooth muscle cells only with damage to the internal elastic lamina, causing a sausage-like constriction. When the internal elastic lamina was damaged smooth muscle cells were persistently depolarized. Dr. Bevan said he believes that the damage caused to the endothelium and the internal elastic lamina could be permanent, producing a marked and sustained artery contraction.

Dr. Richard White talked on the pharmacological action of a number of substances on cerebral vessels. A large number of substances are vasoactive but their action depends greatly on how they are administered. Some agents applied topically produced one reaction, but when given intravenously produced another reaction. Amines, other protein derivatives, polypeptides, lipids and prostaglandins all produced vasospasm and most of the substances that produce vasoconstriction had an effect on prostaglandins. He also mentioned that the metabolites of many of the substances may cause vasoconstriction and may cause a synergistic action producing spasm. More than 30 substances have been demonstrated to produce spasm. Agents which are believed to produce vasodilation, in different concentrations and with different types of application, may cause spasm.

### Therapy

Dr. Frederick Simeone, going over therapeutic concepts in the management of spasm, pointed out the extremely large number of agents which have been suggested to reduce or stop spasm. These included isoproterenol, phenoxybenzamine, priscoline, regitine, reserpine, kanamycin, etc. All have been tried but no study was definitive. He suggested that the most effective regimen currently available was reserpine and kanamycin. If these were given in advance to patients following subarachnoid hemorrhage spasm appeared to be prevented. He said he believed that they acted mainly by reducing serotonin.

There is a suggestion that increasing the blood pressure seemed to be effective in getting a maximum amount of blood to pass the area of spasm. This treatment had some risk in patients who had not had surgery to obliterate the aneurysm. He mentioned giving blood to increase blood volume and thereby increasing blood pressure. This treatment seemed to improve patients and reduce spasm.

Dr. Nicholas Zervas reported that in his use of reserpine and kanamycin in a controlled study 28 patients with subarachnoid hemorrhage, who did not receive this treatment, all developed spasm. Only 1 of 26 who had the treatment developed vasospasm. Dr. Zervas also said that increased blood volume with transfusion seems to improve the clinical state of patients with spasm and postulated that the increase of blood volume associated with hypertension might stretch vessels and reduce spasm. This required excess transfusion with addition of 4 units of blood which produced a prolonged elevation in blood pressure.

Dr. Arthur Waltz questioned whether elevating blood pressure would reduce vasospasm. Dr. Robert Grubb said he had increased blood volume in patients with subarachnoid hemorrhage to counteract spasm. He said he had not been able to demonstrate major decreases in cerebral blood flow in these seriously ill patients. Dr. Richard Fraser mentioned that the angiogram does not usually give good evidence of distal perfusion for patients with spasm. He did not believe there was currently any good explanation for spasm. It was largely confined to patients with aneurysmal rupture, with subarachnoid hemorrhage.

Arterial spasm was uncommon following obvious vascular damage accompanying brain tumor removal or bleeding following head injury. He said he was reluctant to accept the idea that arterial spasm was the cause of delayed neurological defects.

Dr. C. Miller Fisher cited his experience in correlating evidence on angiography of cerebral spasm and the clinical state of the patient. While not every patient with evidence of arterial spasm had neurologic deficits following onset of subarachnoid hemorrhage, those who did have a deficit late after onset generally had evidence of arterial spasm on angiogram.

In discussion there was no agreement on the relationship of spasm to neurologic defect. Initially much of the neurologic defect is related to the damage produced by bleeding into the brain. For those patients who arrive at the hospital with subarachnoid hemorrhage without evidence of neurologic defect and who develop neurologic defects, some 3 or so days after, the issue is still not settled whether this neurologic change is due to spasm or to rebleeding. Dr. Fisher felt that there was a connection between the appearance of severe spasm on cerebral angiograms and the degree of neurologic deficit as seen in patients with subarachnoid hemorrhage. Some discussants expressed concern that
one could really not tell from clinical examination whether a patient had re-bleed or whether his symptoms were due to vascular spasm. Although the angiogram showed vessel constriction there was not a one-to-one correlation with the clinical picture.

Stroke and CV System

The sixth session was devoted to the effect of stroke on the cardiovascular system with Dr. Thomas Price as moderator. Dr. Walter Randall, talking on the effect of the autonomic nervous system on cardiac arrhythmias and conduction, described his experiments on the dog heart. The sympathetic nervous system innervated specific portions of cardiac muscle and specific vessels in a particular region. Stimulation of the sympathetic nervous system augmented cardiac muscle contractility locally. Vagal stimulation largely acted on the heart by altering the conducting system. His data were obtained by heart denervation leaving 1 or 2 remaining sympathetic cardiac nerves, tracing their sites of innervation, and examining their action on the cardiac function. This indicated that the heart had very specific sympathetic innervation and damage to the brain and to the sympathetic nervous system can affect specific heart areas.

Dr. G. Michael Vincent, discussing cardiac electrophysiologic abnormalities in stroke, pointed out that the usual ECG abnormalities in stroke were prolongation of the QT interval, large area T waves, but generally normal QRS complexes. The common rhythm disturbances were ventricular tachycardia or flutter and, occasionally, ventricular fibrillation. Autonomic stimulation causes local changes in cardiac physiological function and changes in the electrocardiogram. Parasympathetic stimulation tended to shorten the action potential and prolong conduction at the A-V node.

Sympathetic stimulation tends to enhance ventricular contractility and potassium-calcium conduction and to shorten the action potential. Stimulation causes a conduction defect rather than a structural change in heart muscle. It also causes changes in diastolic repolarization and a change in the firing rate of cells.

Parasympathetic stimulation increased potassium conductance and sympathetic stimulation decreased it. Dr. Vincent reported that when the brain recovers following a stroke or subarachnoid hemorrhage the abnormal stimulation of cardiac nerves and the arrhythmia thus produced disappear.

Stroke and Lung Function

Dr. Thomas Lloyd discussed the effect of stroke on lung function and the pulmonary circulation. Following cerebral damage a number of changes in breathing may take place, including apnea, hyperpnea, and Cheyne-Stokes respiration. Patients with stroke generally tended to overbreathe without the usual accompanying blood gas concentration changes, which indicated to him that there were some sections of lung which were undergoing a change in ventilation-to-perfusion ratios and that there was underperfusion with reduction of oxygen content in some lung areas. He said the most common pulmonary change that has been described with stroke, and especially with increased intracranial pressure, was pulmonary edema. He added that pulmonary edema was always related to some increase in capillary permeability to water. But alveolar permeability was not altered and the fluid moved into the intracellular space but not into the alveoli. Pulmonary edema was found most often with increased intracranial pressure and increased sympathetic outflow. Experimentally, increased intracranial pressure pulmonary edema can be blocked by interfering with sympathetic discharge from the brain. Increased sympathetic discharge, in causing pulmonary edema, produced a marked peripheral constriction forcing more blood into the lungs, thereby increasing the end systolic resistance and increasing pulmonary arterial pressure. The fundamental cause of pulmonary edema was an overperfusion of the lungs which may cause pulmonary capillary endothelial damage. There is some indication of neurogenic regulation of capillary permeability since the fluid in pulmonary edema following stroke or increased intracranial pressure often had a high protein content, supporting the notion of increased capillary permeability.

Dr. Robert Joynt talked on the effect of stroke on catecholamine output in the cardiovascular system. He cited what appeared to be a stress response following stroke with elevated urinary catecholamines and elevated plasma cortisol, both being quantitatively related to the severity of the patient's stroke. These changes ultimately appeared to be related to the long-range prognosis. Patients with subarachnoid hemorrhage generally had a higher output of catecholamines and corticosteroids. But the difference in elevations of these substances in subarachnoid hemorrhage, when compared with other types of stroke, was not significant. There was no difference in output of steroids or catecholamines in strokes involving the vertebrobasilar system when compared with stroke involving the brain supplied by the carotid distribution. Arrhythmias with subarachnoid hemorrhage occurred in those patients with high catecholamine outputs and propranolol in such patients may block the heart response to high catecholamine levels.
Participants in the 11th Princeton Conference on Cerebrovascular disease were:

Robert H. Ackerman, M.D.
Departments of Radiology and Neurology
Massachusetts General Hospital
Boston, Massachusetts 02114

George S. Allen, M.D., Ph.D.
Assistant Professor of Neurosurgery
The Johns Hopkins Hospital
Baltimore, Maryland 21205

Adelbert Ames, III, M.D.
Professor of Physiology
Department of Surgery
Harvard Medical School
Boston, Massachusetts 02114

H. J. M. Barnett, M.D.
Professor and Chairman
Department of Clinical Neurological Sciences
University of Western Ontario
London, Ontario, Canada

Jean D. Benedict, M.S.
Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health
Bethesda, Maryland 20014

John A. Bevan, M.D.
Professor of Pharmacology
University of California School of Medicine
Los Angeles, California 90024

Otis Blaumanis, Ph.D.
Department of Neurology
University of Maryland School of Medicine
Baltimore, Maryland 21201

Robert S. Bourke, M.D.
Professor and Chairman
Division of Neurosurgery
Albany Medical College
Albany, New York 12208

Derek A. Bruce, M.B., Ch.B.
Associate Neurosurgeon
Children's Hospital of Philadelphia
Assistant Professor Neurosurgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104

John J. Caronna, M.D.
Associate Professor of Neurology
University of California School of Medicine
San Francisco, California 94143

Maynard M. Cohen, M.D., Ph.D.
Jean Schwepe Armour Professor and Chairman Department of Neurological Sciences
Rush-Presbyterian St. Luke's Medical Center
Chicago, Illinois 60612

John A. Correia, Ph.D.
Assistant Physicist
Department of Radiology
Massachusetts General Hospital
Boston, Massachusetts 02114

Robert M. Crowell, M.D.
Assistant Professor of Surgery
Harvard Medical School
Boston, Massachusetts 02114

James N. Davis, M.D.
Associate Professor of Medicine (Neurology) and Pharmacology
Duke University Medical Center
VA Hospital
Durham, North Carolina 27705

Professor George H. du Boulay
The National Hospitals for Nervous Diseases
Queen Square London WCIN 3 BG
England

Mark L. Dyken, M.D.
Professor and Chairman
Department of Neurology
125 Emerson Hall
Indiana University School of Medicine
1100 West Michigan Street
Indianapolis, Indiana 46202

Alan M. Edelson, Ph.D.
President — Raven Press
1140 Avenue of the Americas
New York, New York 10036

John Eichling, Ph.D.
Associate Professor of Radiology
Washington University Medical School
St. Louis, Missouri 63110

William S. Fields, M.D.
Professor and Chairman
Department of Neurology
University of Texas Health Science Center
Houston, Texas 77030

C. Miller Fisher, M.D.
Professor of Neurology
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts 02114

Richard A. R. Fraser, M.D.
Associate Professor — Neurosurgery
Cornell University Medical School
New York, New York 10021

Julio Garcia, M.D.
Professor of Pathology
University of Maryland School of Medicine
Baltimore, Maryland 21201

Myron D. Ginsberg, M.D.
Assistant Professor of Neurology
University of Pennsylvania School of Medicine
3400 Spruce Street
Philadelphia, Pennsylvania 19104

Murray Goldstein, D.O., M.P.H.
Director, Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health
Bethesda, Maryland 20014

Patricia A. Grady, Ph.D.
Instructor, Department of Neurology
University of Maryland School of Medicine
Baltimore, Maryland 21201

Jerome G. Green, M.D.
Director
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
Bethesda, Maryland 20014

Leon Jack Greenbaum, Jr., M.D.
Staff Scientist
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health
Bethesda, Maryland 20014
<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert L. Grubb, Jr., M.D.</td>
<td>Associate Professor of Neurological Surgery</td>
</tr>
<tr>
<td>Washington University School of Medicine</td>
<td></td>
</tr>
<tr>
<td>St. Louis, Missouri 63110</td>
<td></td>
</tr>
<tr>
<td>James H. Halsey, Jr., M.D.</td>
<td>Professor and Chairman</td>
</tr>
<tr>
<td>Department of Neurology</td>
<td></td>
</tr>
<tr>
<td>University of Alabama Medical Center</td>
<td></td>
</tr>
<tr>
<td>Birmingham, Alabama 35204</td>
<td></td>
</tr>
<tr>
<td>Maury L. Hanson, Jr., M.D.</td>
<td>Stroke and Trauma Program</td>
</tr>
<tr>
<td>National Institute of Neurological and Communicative Disorders and Stroke</td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health Bethesda, Maryland 20014</td>
<td></td>
</tr>
<tr>
<td>William K. Hass, M.D.</td>
<td>Professor of Neurology</td>
</tr>
<tr>
<td>New York University School of Medicine</td>
<td></td>
</tr>
<tr>
<td>550 First Avenue New York, New York 10021</td>
<td></td>
</tr>
<tr>
<td>Albert F. Heck, M.D.</td>
<td>Professor and Chairman</td>
</tr>
<tr>
<td>Department of Neurology</td>
<td></td>
</tr>
<tr>
<td>University of Tennessee Center for the Health Sciences Memphis, Tennessee 38163</td>
<td></td>
</tr>
<tr>
<td>Albert Heyman, M.D.</td>
<td>Professor of Neurology</td>
</tr>
<tr>
<td>Duke University Medical Center Durham, North Carolina 27710</td>
<td></td>
</tr>
<tr>
<td>Sadek Hilal, M.D.</td>
<td>Professor of Radiology and Director Neuroradiology</td>
</tr>
<tr>
<td>Neurological Institute of New York 710 West 168th Street New York, New York 10032</td>
<td></td>
</tr>
<tr>
<td>Konstantin-Alexander Hossmann, M.D.</td>
<td>Professor, Experimental Neurology Max-Planck-Institute for Brain Research</td>
</tr>
<tr>
<td>Cologne-Merheim, Federal Republic of Germany</td>
<td></td>
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<tr>
<td>J. O'Neal Humphries, M.D.</td>
<td>Robert L. Levy Professor of Medicine and Cardiology</td>
</tr>
<tr>
<td>The Johns Hopkins School of Medicine</td>
<td></td>
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<tr>
<td>Baltimore, Maryland 21205</td>
<td></td>
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<tr>
<td>Frans Jöbsis, Ph.D.</td>
<td>Professor of Physiology</td>
</tr>
<tr>
<td>Duke University Durham, North Carolina 27710</td>
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<tr>
<td>Robert J. Joynt, M.D.</td>
<td>Professor and Chairman</td>
</tr>
<tr>
<td>Department of Neurology</td>
<td></td>
</tr>
<tr>
<td>University of Rochester Rochester, New York 14642</td>
<td></td>
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<tr>
<td>Robert Katzman, M.D.</td>
<td>Professor and Chairman</td>
</tr>
<tr>
<td>Department of Neurology</td>
<td></td>
</tr>
<tr>
<td>Albert Einstein College of Medicine New York, New York 10001</td>
<td></td>
</tr>
<tr>
<td>Arthur C. Klassen, M.D.</td>
<td>Professor and Director</td>
</tr>
<tr>
<td>Division of Adult Neurology</td>
<td></td>
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<tr>
<td>University of Minnesota Medical School</td>
<td></td>
</tr>
<tr>
<td>Minneapolis, Minnesota 55455</td>
<td></td>
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<tr>
<td>Dr. Igor Klatzo</td>
<td>Chief, Laboratory of Neuropathology and Neuroanatomical Sciences</td>
</tr>
<tr>
<td>National Institute of Neurological and Communicative Disorders and Stroke Bethesda, Maryland 20014</td>
<td></td>
</tr>
<tr>
<td>Kiyuya Kogure, M.D.</td>
<td>Associate Professor of Neurology</td>
</tr>
<tr>
<td>University of Miami School of Medicine</td>
<td></td>
</tr>
<tr>
<td>Miami, Florida 33152</td>
<td></td>
</tr>
<tr>
<td>David E. Kuhl, M.D.</td>
<td>Professor of Radiological Sciences</td>
</tr>
<tr>
<td>Chief, Division of Nuclear Medicine U.C.L.A. School of Medicine Los Angeles, California 90024</td>
<td></td>
</tr>
<tr>
<td>John F. Kurtzke, M.D.</td>
<td>Professor of Neurology and Community Medicine</td>
</tr>
<tr>
<td>Georgetown University School of Medicine and Chief Neurology Service V. A. Hospital Washington, D.C. 20422</td>
<td></td>
</tr>
<tr>
<td>William M. Landau, M.D.</td>
<td>Professor and Head</td>
</tr>
<tr>
<td>Department of Neurology</td>
<td></td>
</tr>
<tr>
<td>Washington University School of Medicine St. Louis, Missouri 63110</td>
<td></td>
</tr>
<tr>
<td>David E. Levy, M.D.</td>
<td>Assistant Professor of Neurology</td>
</tr>
<tr>
<td>New York Hospital — Cornell Medical Center New York, New York 10021</td>
<td></td>
</tr>
<tr>
<td>Abraham M. Lilienfeld, M.D., M.P.H.</td>
<td>University Distinguished Service Professor of Epidemiology</td>
</tr>
<tr>
<td>The Johns Hopkins University School of Public Health Baltimore, Maryland 21205</td>
<td></td>
</tr>
<tr>
<td>Thomas C. Lloyd, Jr., M.D.</td>
<td>Professor of Medicine and Physiology</td>
</tr>
<tr>
<td>Indiana University Medical Center</td>
<td></td>
</tr>
<tr>
<td>Indianapolis, Indiana 46202</td>
<td></td>
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<tr>
<td>Alan Lockwood, M.D.</td>
<td>Assistant Professor of Neurology</td>
</tr>
<tr>
<td>University of Miami School of Medicine</td>
<td></td>
</tr>
<tr>
<td>P. O. Box 520875 Biscayne Annex Miami, Florida 33132</td>
<td></td>
</tr>
<tr>
<td>Fletcher H. McDowell, M.D.</td>
<td>Professor of Neurology</td>
</tr>
<tr>
<td>Cornell University Medical College</td>
<td>New York, New York 10021</td>
</tr>
</tbody>
</table>
F H McDowell and C H Millikan

Stroke. 1978;9:429-439
doi: 10.1161/01.STR.9.5.429
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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