Progress in Cerebrovascular Disease

Experimental Ischemic Stroke: A Review

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THE HUMAN SYNDROME OF STROKE consists of the abrupt development of a focal neurologic deficit whose origin can be traced to either the occlusion of a cerebral vessel (usually arterial), or the spontaneous rupture of an intracranial artery with consequent hemorrhage in the brain parenchyma or in the subarachnoid space.1

Retrospective analyses of large groups of stroke patients have demonstrated that the vast majority were afflicted with one of three anatomical lesions: about 75% of all strokes are the clinical expression of brain infarctions; large, usually single, brain hemorrhages constitute the background for about 11%; and primary, non-traumatic, subarachnoid hemorrhages make up almost 5% of all strokes.2-4

Brain infarction is a localized destructive lesion attributable to the occlusion of a brain vessel, usually arterial. This selective review of experimental stroke is based on an analysis of medical literature dealing with the induction of localized brain lesions through the occlusion of a single artery. Data from experiments based on multiple vessel occlusion, changes in systemic blood pressure, exposure to nitrogen atmosphere, seizures, and others are not included in this review because the resemblance between these and the condition of brain infarction in humans has not been demonstrated.

On account of its frequency, ischemic stroke is the most important condition of this group; therefore, it is reasonable to focus attention on the analysis of stroke models in which the neurologic deficit is the result of a single-artery occlusion. According to Descartes,5 one's understanding of the whole (in this case, ischemic stroke) may be significantly enhanced by dividing each part into several small components. In an attempt to achieve such improved understanding, the bibliography on ischemic stroke is reviewed under the following separate headings, i.e.:

(A) the most relevant and reproducible model of stroke,

(B) experimental methods to induce ischemic stroke,

(C) the evolution (pathophysiology) of ischemic stroke

1. Changes in circulation and electrical activity,

2. Changes in vascular reactivity,

3. Biochemical/metabolic alterations,

4. Edema; changes in BBB permeability and intracranial pressure,

5. Histologic and histochemical features.

(D) attempts to modify the outcome of evolving brain infarctions.

A. The Most Relevant and Reproducible Model

The laboratory analysis of the phenomena leading to a brain infarction requires an animal model in which: (a) a single-artery can be reproducibly occluded, (b) the vascular occlusion results in predictable changes in blood flow, i.e.: focal or regional ischemia, (c) barbiturates are not used at the time of the arterial occlusion; in this way, the corresponding neurologic deficits can be easily ascertained. Moreover, the potential interference with blood flow determination and the barbiturate protection from the effect of ischemia may be avoided, (d) inducement of the above conditions should always result in a parenchymal lesion closely resembling a human brain infarction, and (e) the method of arterial occlusion should be compatible with subsequent reperfusion of the ischemic territory.

The relevance of the model of single-artery occlusion to the human condition of ischemic stroke was the subject of ample debate at an International Conference on Cerebrovascular Diseases.6

The behavior, motor and sensory integration, amount of necortex, and construction of the cerebral vasculature are all important factors dictating the selection of non-human primates as models of ischemic stroke.7 The erect position, the non-osseous dural ten-}

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malities, seizures, and impairment of consciousness (which are not common features of human ischemic stroke) often accompany cerebral ischemia in these animals.

B. Experimental Methods to Induce Ischemic Stroke

Ligation of the *cervical* arteries does not induce significant changes in the brain circulation of most animal species, including humans. This is because in most species there are numerous end-to-end anastomoses that establish connections between branches of the internal and the external carotid arteries. The absence of posterior communicating arteries, among certain breeds of gerbils (*Meriones unguiculatus*), makes this species susceptible of developing hemispheric ischemia after unilateral carotid ligation. However, there are significant drawbacks, mentioned above, that make most rodents less than ideal models of ischemic stroke.

Unilateral, temporary carotid ligation produces only transient neurologic deficits in a minority of patients subjected to this operation for the treatment of intracranial aneurysms; but, the neurologic deficits disappear when the artery is re-opened, thus showing that reperfusion can reverse the clinical effects of ischemia. The exact time during which changes of neuronal function or structural damage produced by ischemia remain reversible has not been established. In monkeys, transient middle-cerebral artery (MCA) occlusion (1-2 hr) results in mild or no neurologic deficit, 4 hr in moderate deficits, and 6-8 hrs in severe deficit. This suggests that ischemia secondary to an arterial occlusion is not an all-or-none phenomenon; rather, it suggests that the longer the occlusion, the more neurons are lethally injured and the worse is the functional deficit.

Early descriptions of surgical methods that permit occlusion of an intracranial artery in the dog have been variously modified for the purposes of (a) minimizing injury to the brain (b) avoiding exposure of the intracranial contents to the atmosphere, (c) adapting the method to more than one animal species, (d) adapting the arterial-occlusion maneuver to unanesthetized animals, and (e) making the surgical technique compatible with transient occlusion, i.e.: allowing reperfusion. A method to occlude the MCA and induce hemispheric infarction in the rat has been described recently.

A method to embolize an intracranial artery with homologous blood was described in 1955. In these animals, the rate of success in the induction of infarctions was estimated at 80% and the operative mortality at 16%. Since then, improved methods to embolize an MCA that yield close to 100% success have used silicone spheres, silastic materials and others. A tabulation of these and other embolic methods to induce arterial occlusions at predictable sites has been published elsewhere. Injecting emboli (homologous blood or other materials) for the purpose of occluding an MCA avoids even a minimal craniotomy, but unfortunately, the method results in permanent vascular occlusion, i.e.: it precludes reperfusion.

The *transorbital* surgical approach to the initial segment of the middle cerebral artery first described in 1970, although remarkably advanced is not without some effects on the adjacent brain tissue. The reliability of this method to induce either an infarction or transient neurologic deficits makes it a valuable technique for inducing hemispheric ischemia after unilateral carotid ligation. However, there are significant drawbacks, mentioned above, that make most rodents less than ideal models of ischemic stroke.

Angiography confirms that transorbital Middle-Cerebral-Artery Occlusion (MCA-O) leads to a total interruption of the anterograde flow. The same technique demonstrates the leptomeningeal anastomoses that normally exist between branches of the MCA and those of the anterior cerebral and posterior cerebral arteries through which retrograde flow promptly develops. Some of the disadvantages of the transorbital approach to the MCA include: the need for a meticulous surgical orbital intervention, the possibility of injuring the nerve fibers normally found in the adventitia of the MCA, and the creation of a potential CSF fistula. Excessive manipulation of the vessel during surgical exposure and the resulting vasospasm may alter the efficiency of the subsequent collateral blood supply. None of the above disadvantages are as significant as are the: (1) inability to create steady-state conditions in the flow of blood, (2) unpredictability of the resulting circulatory disturbance, and (3) unpredictability of the distribution and size of the lesions. Considerable variability in the severity of ischemia (i.e.: degree of CBF decrease) exists even when surgical procedures are carefully standardized and the physiologic parameters are kept as constant as possible. The enormous variability in the local circulatory conditions, characteristically observed after occluding an MCA at the very same site, is probably explained by the variable types of collateral connections that exist in individual animals. These temporal and spatial circulatory variabilities make the method of MCA-O unsuitable for many of the statistical comparisons that are required in experiments that attempt to predict the evolution of the lesion and to evaluate therapeutic interventions.

C. The Evolution (Pathophysiology) of Ischemic Stroke

The following notes are based on studies conducted on models of focal brain ischemia i.e.: experiments based on the occlusion of a middle-cerebral artery (MCA-O), in either subhuman primates or cats. There are no descriptions of differences in the consequences of an MCA occlusion that can be considered species specific. The presumed mechanisms responsible for
the transition from reversible to irreversible focal ischemic injury are presented under the following headings:

(1) Changes in Circulation, Blood Flow and Electrical Activity

After MCA-O, circulation persists in many of the areas normally supplied by the occluded artery as demonstrated by visualizing fluorescein and carbon black injected intravenously. Peripheral to the area of ischemia, local loss of autoregulation can be demonstrated about one hour after the MCA-O.63, 64

On the cortical surface, over a period of several hours, darkening of venous blood, slowing of the flow and aggregation of circulating blood elements is followed by appearance of focal pallor, arterial spasm, appearance of red blood in veins, perivenous hemorrhages and cerebral edema.35, 56 The data on CBF changes, following a single artery occlusion, are seemingly inconsistent. The variations (or some times contradictions) encountered below probably reflect the applications of different methods to animals of varying ages and species. Another significant factor must be the marked heterogeneity in CBF changes and structural damage that are typical of single artery occlusion.65 Following an arterial occlusion, flow does not begin to fall until the resistance vessels in the affected territory are fully dilated. This is one of the reasons why during focal ischemia, local regulation of blood flow is abolished.37, 58 After MCA-O cortical blood flow is reduced to unmeasurable levels in squirrel monkeys and to approximately one-half of the control values in cats. In some animals, manipulation of the artery alone, is sufficient to reduce cortical flow.57, 59 After MCA-O, CBF in baboons decreases in a highly heterogeneous fashion: only 10–20% drop is observed in the lips of the Sylvian cortex with much more severe changes occurring in the putamen and globus pallidus.4, 26, 53 In squirrel monkeys the changes in local CBF, within the corresponding arterial territory, are multifocally heterogeneous: they vary in the cortex from 20 to 50% of preocclusive levels.56, 60 In the central areas of the ischemic territory, CBF may remain as low as 50% of normal. The effects of focal ischemia (3 hrs duration) on brain ATP and lactate levels compare favorably with the effects of global ischemia of 15 min duration; this suggests that after an arterial occlusion, the period of reversibility may be considerably longer than previously thought.35, 61

In squirrel monkeys the changes in electroencephalographic tracing reflect more accurately the state of the ischemic brain area than do the changes in blood flow, calculated by the xenon 133 method.62 Evoked potential and spontaneous neuronal activity disappear at flow rates of 16–18 ml/100 gm/min.49 Areas where local CBF falls to levels lower than 16 fail to show complete recovery of evoked response; furthermore, brief periods of air ventilation depress evoked responses even more in these areas.53 The EEG begins to flatten at flow values slightly below normal and becomes isoelectric when blood flow decreases below 15 ml/100 gm/min. Evoked potentials begin to decrease at flow values below 20 ml/100 gm/min and are completely suppressed below 15.64

In cats, the neurologic deficits relate best to the degree of tissue change. In gray matter, the decrease in CBF is maximal at 2 days after MCA-O. The results are more variable for the white matter. Hyperemia is evident some times as late as 15 days after the arterial occlusion. Some of this hyperemia is visible in regions of brain showing histopathologic evidence of ischemic damage. Although the CBF is generally decreased in regions showing histologic change, the two do not always correlate well.65 With implanted hydrogen electrodes, five patterns of CBF changes are recorded in cats with unilateral MCA-O; most animals showed lowest CBF values immediately after the arterial occlusion. In a few, the lowest values were recorded two days later.66

Obstruction or absence of circulation through small parenchymal vessels (microcirculation) does not seem to play a major role in the production of an infarction; by the carbon perfusion technique, filling impairment is not detected after 90 min of MCA occlusion, and only slight impairments exist after 3 hrs. Severe microcirculatory obstruction develops after this period of time.49, 65 However, extensive injury to neurons precedes the development of microvasculature obstruction and neuronal destruction is more widespread than impaired perfusion.48, 66

(2) Changes in Vascular Reactivity

Changes in autoregulatory control, within the ischemic territory result in conditions whereby the blood flow parallels mean arterial blood pressure at hypotensive and normotensive levels, but not at hypertensive levels.57 In contrast to the responses obtained from non-ischemic hemispheres, neither aminophylline nor ergotamine tartrate increase CBF in brain made ischemic by MCA-O.69 When regional ischemia is induced by creating spasm in an MCA, local CBF varies indirectly with the severity of spasm before the development of ischemic necrosis. The onset of infarction is marked by permanent depression of local CBF despite recovery of the arterial caliber.70 Increases of ambient PaCO2 result in either no change or paradoxical contraction of the blood vessels within the territory of the occluded artery.71 According to Ott et al.,27 following MCA occlusion in the baboon, regional dysautoregulation (i.e.: absence of appropriate vascular responses to infusion of metaraminol or angiotensin) in infarcted cortex correlates with increased acetylcholinesterase levels in the same zones of cortex and basal ganglia. The onset of this dysautoregulation correlates with the time when increased cholinesterase uptake by the brain is demonstrable. The intravenous infusion of a cholinergic neurotransmitter blocker (eg: scopolamine) restores autoregulation to the ischemic zones. Thus, autoregulation appears to be a myogenic reflex influenced by neurogenic and metabolic mechanisms.71

In cats, occlusion of an MCA stops the corresponding regional CBF for about 30 seconds. Despite a CBF
equal to one-half of the control, cerebral blood volume undergoes excessive recovery overshooting the control levels. "Low perfusion hyperemia" appears more slowly and it is more diverse in the older than in the young groups. Thus, aging seems to decrease the reactivity of the vascular response to ischemia and may impair the integrity of collateral vessels. 73

(3) Biochemical/Metabolic Alterations in Areas of Focal Ischemia

During the early phase of focal ischemia, the regional metabolic responses vary considerably, depending on the reduction of local blood flow. Under chronic conditions, a sharp metabolic and hemodynamic demarcation develops between ischemic and non-ischemic regions. 74

Changes in brain metabolites (lactate, pyruvate, AMP and ADP) after MCA-O of one hour duration are confined to the corresponding arterial territory, but they are unpredictable in both severity and distribution. 43 The gradual decrease in ATP to 55, 35 and 20% of normal levels and the corresponding increase in lactate, 2-4 hrs after MCA-O can be reversed by reperfusion. The correlation of lactate levels with the local blood flow suggests that loss of autoregulation and "luxury perfusion" in focal ischemia of the brain are the result of lactate acid accumulation. 39 Oxygen availability drops promptly after the arterial occlusion and vascular reactivity (autoregulation) is lost during the period of the arterial occlusion, but recovery of the vascular reactivity is demonstrable after long-term survival. 72

Contents of lipid-bound bivalent cations in brain decrease promptly as a consequence of 2 min arterial occlusion. This may be one of the reasons for the dysfunction of plasma membranes. 91 Changes in c-AMP, as early as 3 hrs after MCA-O may mean that, in ischemia an initial alteration of the cell metabolism is caused by plasma membrane perturbations mediated by the altered production of this second messenger. 77

The reduction of ascorbic acid in brain as a function of ischemic time has been interpreted as indicative of its consumption in the quenching of free radicals. 77

A dual ischemic threshold is described for neuronal function, the threshold for release of K+ being clearly lower than the one needed for complete electrical failure. These observations support the concept of an ischemic penumbra during which neurons may remain structurally viable, but are functionally inactive. 79 That neurons can survive for some time in this sublethal state of injury is evidenced by the observation that reperfusion can restore evoked potential, as well as normalize extracellular K+ and pH. 78 Extracellular potassium rises when CBF drops below 8-10 ml/100 gm/min49 and a disturbance of net water and electrolyte content becomes evident at flow values below 10-15 ml/100 gm/min. 32, 32

After MCA-O (60 min), local increases of C-14 deoxyglucose uptake are associated with mild to moderate anaerobic perturbations of metabolite levels. Brain regions showing decreased deoxyglucose uptake invariably are depleted of ATP and phosphocreatin. Thus, suppression of glucose metabolism is restricted to the most severely ischemic areas. 47

4. Edema; Changes in BBB Permeability and Intracranial Pressure

An immediate increase in brain volume after inducing focal ischemia is due to vasoparalysis (i.e.: dysautoregulation); this is followed by "metabolic" edema that is probably caused by a breakdown in energy metabolites. At a later time (4-6 hrs) ischemic brain edema may be associated with breakdown in vascular permeability to proteins. 40

During the initial three hours of ischemia, increase in water and sodium contents are almost exclusively confined to the gray matter. After 12-48 hrs water retention and sodium increase become progressively more pronounced in the white matter. 79 Maximal accumulation of fluid with fluxes in sodium/potassium (in reciprocal directions) occurs at 12 hrs in the cortex and in the putamen at 24 hrs. After 48 hrs and in spite of irreversible injury to the parenchyma, partial reversal in water retention and abnormalities in electrolytes is observed in the gray matter. The adjacent white matter shows progressive water increases from 12-48 hrs; definite increases in sodium with decreases in potassium are not observed in the white matter before 48 hrs. 80

Brain/blood ratios for circulating substances that normally do not cross the blood brain barrier (pertechnetate and albumin) are greatest in infarcted tissue. High ratios for these substances indicate a normal extravascular distribution of pertechnetate. These ratios increase as early as 4 hrs after MCA-O, become maximal at 4-7 days and remain high until 20 days. The distribution of water does not have the same temporal or spatial distributions of macromolecules and other substances. 37 Edema associated with a leakage of serum proteins develops only after several hours and at a time when most brain tissues presumably are irreversibly damaged. 49, 81 Permanent MCA-O (1-48 hrs) only exceptionally causes extravasation of circulating Evans blue, but temporary occlusion of 4 hrs, followed by 2 hr reperfusion frequently induces exudation of the tracer, particularly in the gray matter. Extravasation of circulating proteins during the first three weeks is related to the size of the area of necrosis, but restitution of the BBB occurs after three weeks irrespective of the infarction size. 81 No evidence of obstruction to albumin and erythrocyte transit was seen in the brain microcirculation after MCA-O of 6 hr despite impaired filling with carbon particles. 82

Brain scintigraphy (in monkeys) becomes positive after two weeks and regresses to normal approximately 6 weeks after MCA-O. The increased radioisotope uptake is related to neovascularization around the infarct. In the late stages, decreased vascularity, gliosis and cavitation are the main factors determining decrease of radionuclide penetration. 83

Comparing animals in which extradural pressure rises, after MCA-O, against those in which it does not,
the most important difference noted was in regional oxygen availability. Animals in which extraludal pressure rises have a recovery of regional oxygen availability slower and less complete than the others. Raised intracranial pressure after MCA-O is first recorded, by epidural transducer about 4 hrs after the arterial occlusion, although occasionally it may occur earlier than that. Therefore, the designation acute neuronal injury may be more accurate and descriptive. The numerous designs applied to neurons injured by incomplete ischemia probably reflect the wide range of ways in which these cells react to changes in blood flow depending upon their histochemical make up, the severity and duration of the ischemia, and the effects of reperfusing a previously ischemic cell.

In mammalian cerebral cortex, six different groups of neurons, topographically unrelated to one another, have been identified on the basis that each group possesses characteristic energy-converting systems. Ischemia is known to induce prompt energy failure thus, it is possible that under comparable ischemic conditions, those neuronal groups whose function depends primarily on high energy-converting systems are more susceptible to be injured than those that do not.

MCA-O typically induces changes in blood flow that are "severe" in the area of the striatum, and, by comparison, "moderate" in the cerebral cortex. This can be readily explained by the presence of abundant collateral connections on the hemispheric surface and the absence of the same in the basal ganglia area. Two extremes in a spectrum of morphologic changes have been described at the striatum and the insular cortex after MCA-O: complete necrosis (including neurons, glia and vascular elements) is commonly observed in the basal ganglia, whereas selective necrosis (usually limited to neurons) has been noted in the cortex. Similarly, in an evolving brain infarction two clearly separate areas of tissue responses have been described: a central one where blood flow is presumed to be the lowest demonstrates uniform and diffuse coagulation necrosis; in contrast, at the periphery, where some blood flow presumably is retained, reactive changes in astrocytes, proliferation of capillaries and presence of inflammatory cells is easily observed.

When the element of time is entered into the estimate of ischemic severity a statistically significant correlation is observed between the percent of dead neurons at a given site and the severity of the ischemic insult (i.e.: the percent decrease in local CBF). This correlation can be demonstrated also between the severity of local edema and the number of lethally injured neurons. Obstruction of the micro-vasculature in a model of strangulation has prompted studies of vascular patency within the territory of an occluded MCA. Numerous observations indicate that after MCA-O, the obstruction of the capillaries and metarterioles takes several hours to develop. Plasmapheresis does not develop after MCA-O of up to 6 hr duration. In other words, when the impaired flow of particles becomes apparent, extensive and irreversible injury is already demonstrable in many neurons. Abnormalities in the microvasculature have been held responsible for the edema of ischemia. Functional derangements of water and ionic transport (in the absence of macromolecule leakage) clearly develop early within the ischemic territory, but these abnormalities occur independent of structural alterations in the majority of
the capillaries.\textsuperscript{10} Focal brain ischemia, secondary to MCA-O (2 hours) followed by 24 hours of reperfusion leads to an initial dilatation and rupture which are more marked in those areas where the ischemia is more severe, i.e. where the CBF values are lowest for the longest periods of time.\textsuperscript{110}

In addition to altering the appearance of the neuronal perikaryon, focal brain ischemia has been shown to induce synaptic swelling, astrocytic enlargement, widening of the extracellular space, and possibly, axonal enlargement.\textsuperscript{57, 111, 112} Astrocytic hypertrophy and hyperplasia are among the most striking features of focal (incomplete) ischemia; such glial response clearly sets apart incomplete ischemia (either focal or transient global) from the situation of complete irreversible ischemia. The marked increase in potassium in the extracellular space and the corresponding fall in sodium/calcium that characterize incomplete ischemia\textsuperscript{54, 78} may stimulate astroglial hypertrophy and hyperplasia as suggested by observations made in cultured astrocytes and microdissected glial cells.\textsuperscript{113} Morphometric studies suggesting increases in the size and numbers of astrocytes have been reported in rat brains made transiently ischemic by multiple vessel occlusion.\textsuperscript{114}

D. Attempts to Modify the Outcome of Evolving Brain Infarctions

The classical dictum that circulatory interruption of a few minutes duration is synonymous with irreversible injury to the brain\textsuperscript{115} must be tempered by the knowledge that (1) arterial occlusions induce incomplete ischemia which is reflected in heterogeneous, unpredictable changes in blood flow, 51, 65, 116 (2) ischemic injury to neurons is selective and progressive or time-dependent, i.e.: the number of neurons injured ten minutes after MCA-O is larger than the number killed at five minutes, but smaller than the number lethally injured by fifteen minutes of ischemia.\textsuperscript{36, 48, 117} and (3) the period required for neuronal ischemic injury to become irreversible (i.e.: to induce permanent loss of function) is probably longer than a few minutes.\textsuperscript{118}

Thus, attempts to induce therapeutic modification of an evolving brain infarction continue to receive considerable attention. According to Hossmann,\textsuperscript{24} the primary therapeutic objectives in ischemic stroke may be to prevent the breakdown of energy-producing metabolites and to preserve nerve cell membrane polarization. These, he believes, can be achieved by increasing collateral blood flow, and lowering the energy requirements of the ischemic tissue. Improving flow requires a selective decrease of the collateral vessels resistance or an increase of the local perfusion. Flow may be improved also by decreasing blood viscosity or reducing ischemic brain edema.\textsuperscript{22}

Yatsu\textsuperscript{119} has suggested three major categories of drugs that may be useful during the acute stage of human ischemic stroke, i.e.: (1) antiedema drugs: steroids and dehydrating agents such as mannitol, urea, and glycerol. (2) anticoagulants (heparin, coumadin) and antiplatelet aggregation drugs (aspirin and penta-

To the above list of medical or chemical therapies, one may add surgical interventions that attempt to re-establish circulation to the ischemic site, i.e.: reperfusion. Several of these therapeutic measures have been applied to experimental ischemic strokes. The results of many of these attempts are either inconclusive or controversial, partly because of the difficulties inherent in measuring a brain infarction, during its acute stage, and the inability to predict how extensive the infarction would have been, in the absence of therapeutic intervention. Most attempts to modify the outcome of ischemic brain lesions are based on comparing features of the ischemic lesions in animals receiving a specific treatment against the nature of the ischemic lesions developing in those animals that either were left untreated or were treated with a placebo. The very heterogeneous and unpredictable course of events set in motion by an arterial occlusion, make the interpretation of these experiments difficult and inconclusive. Also, in many instances, the presumed protection given by a drug is predicated on its being administered before the arterial occlusion in induced.

The mortality and morbidity of monkeys with MCA-O were reduced by reopening the vessel no later than 3 hours.\textsuperscript{17, 56} Administration of pentobarbital at high doses, either before or shortly after MCA-O, results in significantly less infarction.\textsuperscript{46, 120, 121, 122} The protective effect of barbiturates in preventing ischemic edema is not entirely related to their effect on blood flow and metabolism.\textsuperscript{123} Methohexital significantly reduces the rate of decrease of the evoked potential for a given flow below the ischemic threshold.\textsuperscript{54} Administration of an imidazole derivative in combination with pentobarbital results in brain infarctions of small dimensions.\textsuperscript{124}

The metabolic type of post-ischemic brain edema supposedly can be reduced by means similar to those used in post-ischemic edema i.e.: osmotherapy with glycerol, sorbitol, mannitol, or concentrated albumin.\textsuperscript{74}

Large parenteral doses of dexamethasone, administered after MCA-O, do not alter the brain water content, except in areas of necrosis.\textsuperscript{123} Dimethyl sulfoxide (DMSO), given after MCA-O, significantly decreases morbidity when compared to the no treatment group or the group treated with dexamethasone.\textsuperscript{44} Mannitol has a protective effect upon the acute ischemic brain injury as suggested by histologic analysis.\textsuperscript{126, 127} The beneficial effects of mannitol are, however, short lived.\textsuperscript{128} Glycerol may reduce intracellular edema.\textsuperscript{129} Acute systemic hypertension, induced before MCA-O, results in larger cerebral infarctions than would be expected in normotensive animals.\textsuperscript{130} Brain infarctions are smaller when the occluded arteries are reopened within 6 hours of MCA-O and the animals are given low molecular weight dextran.\textsuperscript{131} Infusion of low-molecular-weight dextran, before MCA-O, results in infarctions of small dimensions.\textsuperscript{132} Heparin and hyperventilation, added to
low molecular weight dextran, result in considerable improvement of the microvascular filling.\textsuperscript{133} Prolonged and moderate body hypothermia exerts serious detrimental effects on cats and monkeys with MCA-O.\textsuperscript{134}

Reperfusing a previously ischemic territory, after an as yet undetermined critical period, may be deleterious, i.e.: it may induce local bleeding.\textsuperscript{135} Fluosol-DA may have a protective effect on acute cerebral ischemia.\textsuperscript{136}

Future therapeutic trials may attempt, in addition, to neutralize the factor(s) that influence the transition from sublethal to irreversible ischemic injury. Significant evidence exists pointing to sublethal neuronal injury within the territory of the occluded MCA, as late as 3 hr after the artery is occluded.\textsuperscript{137} Regrettably, at present most therapeutic interventions (both in animals and humans) are conducted without the ability to monitor hemodynamic alterations in the territory of the occluded artery.\textsuperscript{138} Recently published experiments strongly suggest that there exists a linear correlation between degree (i.e.: percent decrease in flow and duration) of local ischemia, and number of lethally injured neurons.\textsuperscript{48} It is reasonable to expect that the recovery of function correlates well with the number of remaining neurons. The concept of an ischemic threshold and a reversible state of ischemic neuronal injury has been designated ischemic penumbra.\textsuperscript{139}

According to Farber and associates\textsuperscript{139} who have studied in vitro and in vivo myocardial and liver cells, two phenomena consistently characterize irreversibly injured ischemic cells: inability to restore mitochondrial function and damage to plasma membranes. Therefore, preventing phospholipid degradation and the associated plasma membrane dysfunction as well as the increased calcium permeability of the sarcoplasmic reticulum, with the infusion of chlorpromazine, lengthens the tolerable period of ischemia for myocardium.\textsuperscript{140}

As indicated before, incomplete brain ischemia is promptly followed by a marked increase in extracellular potassium and a concomitant fall in sodium and calcium.\textsuperscript{50, 75} The increase in intracellular calcium is partly due to a depletion of high energy phosphate compounds but, as indicated by Siesjo,\textsuperscript{141} depletion of energy metabolites alone does not explain all phenomena of irreversible ischemic injury.

The pre-ischemic brain content of glucose determines the severity of lactic acid rise in ischemic brain; it has been postulated that there exists a threshold for lacticosis of 20–25 mmol/Kg with levels above these figures being incompatible with neuronal survival.\textsuperscript{142}

Rainti\textsuperscript{143} has recently summarized the literature on the pathophysiology of brain ischemia. He concludes that in addition to the disturbances in calcium homeostasis, and the accumulation of lactic acid in ischemic tissues, certain conditions initiated by ischemia may explain the propagation of the damage to adjacent territories. These include rise in extra-cellular potassium, release of neurotransmitters that may stimulate neuronal metabolism and release of vasoactive substances capable of disrupting post-occlusive blood flow. Among these vasoactive substances, the effect of some prostaglandins, thromboxane and the leukotrienes are the focus of much current attention. The leukotrienes are the product of the transformation of arachidonic acid into an unstable epoxide intermediate, leukotriene A\textsubscript{4}, which can be converted enzymatically to leukotriene B\textsubscript{4} by addition of glutathione leukotriene B\textsubscript{4} becomes leukotriene C\textsubscript{4}.\textsuperscript{144} The latter is one of the most active of these compounds.

Moncada\textsuperscript{145} recently reviewed the biology and therapeutic potentials of prostacyclin; preliminary studies suggest its future usefulness in the treatment of ischemic stroke.

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