Experimental Regional Cerebral Ischemia in the Middle Cerebral Artery Territory in Primates

Part 2: Effects on Brain Water and Electrolytes in the Early Phase of MCA Stroke

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SUMMARY Acute regional cerebral ischemia was produced in the middle cerebral artery (MCA) territory in monkeys (Macaca mulatta) by selective embolization of the internal carotid (ICA) bifurcation with minimum surgical intervention in the neck under sedated conditions. Two to five hours after embolization, brain water (measurement of dry weight) and tissue concentration of sodium and potassium were determined in the tissues of the Sylvian cortex, putamen and subcortical white matter in the affected MCA territory.

As early as three hours, initial increase in brain water was detected in the samples of the putamen without noticeable change in tissue electrolytes in two of three animals. Gross ischemic swelling of the gray matter, in both the Sylvian cortex and putamen, became obvious in six of eight animals after four to five hours. This swollen gray matter showed marked increase in brain water (up to 36%) swelling, increase in tissue sodium (up to 100% of the control value), and decrease in tissue potassium (down to 56%). On the other hand, edema in the white matter, if present at all, was minimal without detectable change in tissue electrolytes and was always accompanied by much greater (> two to seven times) edema in the gray matter. Thus, the gray matter edema, in both the deep subcortical structures and the cortex, appeared to play the major role in the development of hemispheric swelling of the brain which may begin within hours of the onset of the MCA stroke in monkeys.

Microscopically, the swollen gray matter which showed more than 10% swelling with a definite shift of tissue sodium and potassium content appeared to be dead tissue. However, early edema in the gray matter which showed less than 10% swelling without detectable change in electrolytes might be caused by simple diffusion of water through the dysfunctional capillary wall or cell membrane with or without a permeability gradient between the intravascular cerebrospinal fluid and cerebral tissue compartment and might possibly be reversible.

Introduction

ACUTE MASSIVE ISCHEMIC cerebral edema which may follow the sudden obstruction of a major cerebral artery, usually involving the whole middle cerebral artery (MCA) territory, can be a major cause of death in the acute phase of a stroke or of greater morbidity in the chronic phase. Clinical and experimental studies have shown that cerebral edema following a stroke is at a maximum within a few days and eventually subsides in three weeks if the patient or the experimental animal survives the acute phase, due to the repair mechanism of the brain. The massive cerebral edema at its peak is mainly in the white matter and seems to be "vasogenic" in nature, because the disintegration of the affected tissue is already accomplished by this time. However, the ischemic cerebral edema may begin within hours of the onset of a stroke, suggested clinically by deep hemiplegia and prolonged decreased level of consciousness and signs of transtentorial herniation and shown experimentally by pathological, pathophysiological and chemical analyses of the brain. The major factors which are known to affect the consequences of an acute ischemic stroke are mean arterial blood pressure, PaCO₂, blood viscosity, time course of the ischemic periods and extent of the ischemic area involved. These factors are all related somehow to the degree and extent of the microcirculation in the ischemic brain. The accumulation of an abnormal amount of fluid in the cerebral tissue (cerebral edema) is thought to be responsible for the development or at least for the aggravation of this failed microcirculation and vice versa (no-reflow phenomenon).

An interesting feature of the pathophysiology of the ischemic cerebral edema is that the early edema in the gray matter, described in this communication, seems to develop much before the development of the derangement of the "blood-brain barrier" indicated by the extravasation of blood-borne protein tracers, and before the derangement of the "tight junction" of the capillary endothelium demonstrated by electron microscopy. The present study did not clarify the entire mechanism for the development of early "gray matter edema" following focal cerebral ischemia. However, the authors would like to call attention to the subject of "gray matter edema" which may be quite different from "white matter edema" in terms of its pathophysiology and subsequent treatment.

Methods

The method for the selective embolization of the internal carotid (ICA) bifurcation in monkeys (Macaca mulatta) used to study acute focal cerebral ischemia in the MCA territory has been described in detail in a previous article. Fourteen adult monkeys (3.3 to 5.3 kg of body weight) with selective embolization of the ICA bifurcation were analyzed in this study. These animals were observed clinically over two to five hours while sedated with Sernylan (phencyclidine hydrochloride, maintenance dose of 2 to 4 mg, i.m., every 50 to 70 minutes) and atropine sulfate. Clinical signs and vital functions such as arterial blood pressure, arterial pH, PaCO₂, plasma osmolality and electrolytes, and microhematocrit were monitored periodically. Spontaneous respirations were permitted through an endotracheal tube. Maintenance infusion of Ringer-lactate solution (0.365 ml per minute) was given and urinary output was measured via a bladder...
vertical

The animal was placed on a heating blanket and the temperature was monitored with a rectal probe.

All animals had contralateral deep motor weakness and ipsilateral conjugate eye deviation with horizontal nystagmus shortly after embolization. Of these 14 animals, three showed apparent clinical recovery from the initial deep motor weakness at 50, 80 and 140 minutes respectively.

At the end of the experimental period the CSF was drained by an atraumatic cisternal puncture, the calvarium of the skull was removed, and the sagittal sinus was opened. The animal then was quickly killed by clamping the neck. The whole brain was rapidly removed and the location of the emboli in the base of the brain was confirmed. The brain was then cut coronally in a humid chamber at the level of the anterior commissure for gross pathological study of the sections and further sampling of brain tissues.

Samples were taken from several parts of the brain. However, determinations of tissue dry weight and electrolyte content were concentrated on the tissue samples from the sylvian cortex, putamen and subcortical white matter in the MCA territory to evaluate the relationship between these structures and the acute MCA stroke as well as to obtain large enough samples for analysis and more constant values for dry weight and electrolyte content because of the fairly uniform cell-fiber composition of these tissues.

The sylvian cortex was excised with scissors in a block and a single pure gray matter slice (0.7 to 0.8 mm thick) was cut from this block, without moistening, with a modified Starle-Riggs fresh tissue microtome. The slice was then divided into two pieces, one for dry weight determination (average 240 mg fresh weight) and the other for electrolyte measurement (average 170 mg fresh weight). The samples from the putamen (average 115 mg fresh weight) and subcortical white matter (average 165 mg fresh weight) were cut with hand scissors. Tissue samples were immediately weighed on a microbalance. Similar samples were taken in the same manner from the contralateral hemisphere to be used as controls. The entire procedure was done within 20 minutes of the sacrifice of the animal. The remainder of the brain was fixed in 10% formalin solution and the tissue adjacent to each sample was later stained with hematoxylin and eosin for microscopic examination.

### Analytical Methods

The dry weight of the tissue samples was estimated after drying in an oven at 115°C for 18 hours. The edema of the tissue samples was calculated by the formula originally described by Elliott and Jasper in 1949:

\[
\text{% tissue swelling} = \frac{\text{% dry weight (nonexperimental)} - \text{% dry weight (experimental)}}{\text{% dry weight (experimental)}} \times 100
\]

Tissue concentration of sodium and potassium was determined by emission flame photometry with Li as the internal standard and the values were expressed as μEq/gm fresh tissue. Arterial pH, Pco₂ and Po₂ were determined with a

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**Table 1: Volume of Percentage Dry Weight and Tissue Sodium and Potassium Content of the Cerebral Cortex and Subcortical White Matter**

<table>
<thead>
<tr>
<th>Year/Author</th>
<th>Animals</th>
<th>% Dry weight (nonexperimental)</th>
<th>% Dry weight (experimental)</th>
<th>Subcortical white matter</th>
<th>Subcortical white matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1969/1970/Papoff, McGeachy</td>
<td>Cat (8)</td>
<td>10.2 ± 0.5</td>
<td>32.3 ± 1.7</td>
<td>60.2 ± 5</td>
<td>60.2 ± 5</td>
</tr>
<tr>
<td>1969/1970/Norm, Pippauer</td>
<td>Cat (7)</td>
<td>10.2 ± 0.5</td>
<td>32.3 ± 1.7</td>
<td>60.2 ± 5</td>
<td>60.2 ± 5</td>
</tr>
<tr>
<td>1969/1970/Yates et al.</td>
<td>Dog (20)</td>
<td>10.9 ± 0.3</td>
<td>32.8 ± 1.7</td>
<td>62.8 ± 5</td>
<td>62.8 ± 5</td>
</tr>
<tr>
<td>1969/1970/Schmitt et al.</td>
<td>Mouse (6)</td>
<td>20.2 ± 0.4</td>
<td>32.7 ± 1.7</td>
<td>80.8 ± 5</td>
<td>80.8 ± 5</td>
</tr>
<tr>
<td>1972/1972/Franque, Maimon</td>
<td>Macaque (6)</td>
<td>19.5 ± 0.6</td>
<td>36.4 ± 3</td>
<td>68.5 ± 5</td>
<td>68.5 ± 5</td>
</tr>
<tr>
<td>1970/present authors</td>
<td>Macaque (14)</td>
<td>19.7 ± 0.6</td>
<td>36.4 ± 3</td>
<td>68.5 ± 5</td>
<td>68.5 ± 5</td>
</tr>
</tbody>
</table>

*IL 143 flame photometer.
microelectrode method.† Plasma osmolarity was measured with a precision osmometer.§

Cerebral Edema

Topical differences in the percentage dry weight of different structures were observed, mainly due to the differences in the cell-fiber composition of the different cerebral structures. The slightest amount of macroscopic contamination of the gray matter sample by the white matter resulted in significantly greater percentage dry weight and, conversely, the slightest contamination of the white matter sample by the gray matter resulted in significantly less dry weight. In addition, variability of dry weight values among the individual animals was fairly large as has been observed by other investigators.31 However, the values obtained from the same cerebral structure were fairly close when compared between the hemispheres of an individual animal. For example, the occipital lobe of the monkey is a broad single gyrus (area striata) supplied mainly by the posterior cerebral artery and a pure gray matter slice can be obtained without the risk of CSF contamination. The dry weight of the occipital cortex from the nonexperimental side ranged from 20.68% to 23.04% (21.71% ± 0.75%) and that from the experimental side ranged from 20.22% to 23.37% (21.69% ± 0.90%) \( (N = 14) \). Percentage swelling (brain edema) of the occipital cortex calculated in the individual animal, however, ranged from \(-1.68\%\) to \(2.87\% \) \( (1.12\% ± 1.4\%) \). Therefore, it was thought reasonable to estimate the amount of cerebral edema in each animal.

Topical differences of tissue sodium and potassium content were also observed. Tissue potassium content was significantly lower in white matter than in gray matter because of the smaller cellular component of the former.

Table 1 summarizes the data of percentage dry weight and tissue electrolyte content of the cerebral tissue of different experimental animals by other investigators,26 using basically identical methods to those employed in this study. The dry weight values in this study are similar to those previously reported. Tissue sodium and potassium contents are significantly lower in this study than in the other reports. However, the values of the sodium to potassium ratios are again comparable.

Because of these results, we arbitrarily chose one standard deviation of the control percentage dry weight value as a minimum to identify brain edema. Thus, more than 3.4% swelling of the fresh tissue of the sylvian cortex, more than 5.0% swelling in the putamen and more than 2.7% swelling in the subcortical white matter were considered to indicate significant brain edema.

Results

Acute embolic occlusion of the ICA bifurcation had no significant effect on vital signs and vital functions during two to five hours of the experimental period (Part 1, table 4†). All 14 animals had deep neurological deficits shortly after embolization, but three of them showed apparent clinical recovery during the experimental period. These cases are described individually. However, the extent of the pathology, which in each case was due to ischemia, was variable among the individual animals, and this was reflected by the wide range of standard deviations of percentage dry weight and electrolyte concentration in each experimental group (table 2). No significant pathology was observed in the contralateral hemispheres.

Two Hours’ Ischemia

One animal showed apparent recovery from the initial deep motor weakness at 80 minutes after embolization. The other two animals remained hemiplegic throughout the experimental period. All three brains showed no detectable change in brain water and electrolytes.

### Table 2 Percentage Dry Weight and Tissue Concentration of Sodium and Potassium of Cerebral Tissues of Monkeys With Selective Embolization of the ICA Bifurcation

<table>
<thead>
<tr>
<th>Duration of ischemia (hrs.)</th>
<th>No. animals</th>
<th>% Dry weight</th>
<th>Sodium (μEq/gm fresh tissue)</th>
<th>Potassium (μEq/gm fresh tissue)</th>
<th>Na/K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sylvian cortex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>19.73 ± 0.05</td>
<td>46 ± 3</td>
<td>85 ± 5</td>
<td>54.8 ± 5.2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>19.48 ± 1.11</td>
<td>47 ± 2</td>
<td>82 ± 8</td>
<td>55.2 ± 6.8</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>19.80 ± 0.26</td>
<td>48 ± 2</td>
<td>83 ± 5</td>
<td>58.1 ± 4.7</td>
</tr>
<tr>
<td>4</td>
<td>4 (3)</td>
<td>17.79 ± 1.11</td>
<td>53 ± 10</td>
<td>83 ± 13</td>
<td>66.7 ± 20.2</td>
</tr>
<tr>
<td>5</td>
<td>4 (3)</td>
<td>17.13 ± 2.46</td>
<td>57 ± 24</td>
<td>70 ± 22</td>
<td>102.8 ± 94.4</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>21.30 ± 1.06</td>
<td>43 ± 4</td>
<td>87 ± 5</td>
<td>49.5 ± 4.8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>21.50 ± 0.91</td>
<td>42 ± 3</td>
<td>82 ± 5</td>
<td>51.5 ± 3.1</td>
</tr>
<tr>
<td>3</td>
<td>3 (2)</td>
<td>20.98 ± 1.71</td>
<td>45 ± 2</td>
<td>85 ± 2</td>
<td>52.5 ± 1.5</td>
</tr>
<tr>
<td>4</td>
<td>4 (2)</td>
<td>20.02 ± 1.73</td>
<td>49 ± 11</td>
<td>78 ± 17</td>
<td>68.1 ± 29.2</td>
</tr>
<tr>
<td>5</td>
<td>4 (3)</td>
<td>19.48 ± 1.99</td>
<td>50 ± 11</td>
<td>79 ± 14</td>
<td>63.3 ± 25.6</td>
</tr>
<tr>
<td>Subcortical white</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>32.45 ± 0.86</td>
<td>41 ± 2</td>
<td>66 ± 4</td>
<td>61.7 ± 3.7</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>32.75 ± 1.16</td>
<td>39 ± 1</td>
<td>64 ± 3</td>
<td>61.9 ± 4.4</td>
</tr>
<tr>
<td>3</td>
<td>3 (1)</td>
<td>31.27 ± 0.88</td>
<td>41 ± 1</td>
<td>65 ± 6</td>
<td>61.9 ± 4.9</td>
</tr>
<tr>
<td>4</td>
<td>4 (2)</td>
<td>31.77 ± 0.75</td>
<td>42 ± 1</td>
<td>68 ± 4</td>
<td>61.0 ± 5.0</td>
</tr>
<tr>
<td>5</td>
<td>4 (2)</td>
<td>30.94 ± 1.41</td>
<td>43 ± 2</td>
<td>68 ± 6</td>
<td>66.4 ± 7.7</td>
</tr>
</tbody>
</table>

( ) = number of animals which showed significant amount of percentage tissue swelling.
FIGURE 1. Coronal section of a fresh monkey brain which was exposed to four hours of ischemia in the left MCA territory. Note ischemic discoloration and widening of the sylvian and insular cortices, and loss of distinct junction between the gray and white matter on the affected side. Ischemic discoloration and increased surface area of the basal ganglia are obvious on the left, while the swelling of the white matter is not impressive. There is a slight midline shift from left to right.

Three Hours' Ischemia

One animal showed clinical recovery at 140 minutes after embolization. This animal showed no abnormality in the brain. In all three animals of this group there was no significant difference in the sylvian cortex from the experimental and nonexperimental hemispheres. However, decrease in dry weight was detected in the putamen in two animals which had 5.3% and 8.5% swelling, respectively, without noticeable change in tissue sodium and potassium content. In one of these two brains, edema in the subcortical white matter was also detected (3.9% swelling), again with no significant change in tissue electrolytes.

Four Hours' Ischemia

One animal showed clinical recovery at 50 minutes — first with a grasp response in the affected hand and then slight spontaneous movements of the hand by the end of the experimental period. The sylvian cortex appeared ischemic and showed 13.3% swelling without detectable change in the electrolyte content. The subcortical white matter was normal. Another animal remained deeply hemiplegic throughout the experimental period, but showed no abnormality in the brain water and electrolytes. While the two animals showed marked ischemic swelling in the territory of the affected MCA and a midline shift to the opposite side (fig. 1), the percentage swelling of these specimens was 17.8% and 23.2% in the sylvian cortex, 15.3% and 18.3% in the putamen, and 5.6% and 3.7% in the subcortical white matter respectively. An increase in the tissue sodium, 55 to 67 μEq per gram of fresh tissue, and a decrease in the tissue potassium content, 64 to 61 μEq per gram of fresh tissue, were observed in the specimens from both the sylvian cortex and putamen. The subcortical white matter showed no detectable change in the electrolytes in either case. Micro-pathological study obtained from one of them showed generalized edema, marked swelling of astrocytes and neuronal shrinkage in the gray matter.

Five Hours' Ischemia

The brains which were exposed to five hours of ischemia were similar to those exposed to four hours of ischemia. One brain showed no abnormality. One brain showed 6.6% swelling in the sylvian cortex with no significant change in the electrolytes and 4.0% swelling in the putamen (which was insignificant). One brain showed 9.7% swelling in the sylvian cortex with an increase in tissue sodium (52 μEq per gram fresh weight) and a decrease in tissue potassium content (74 μEq per gram fresh weight), and 12.6% swelling in the putamen with no significant change in the electrolytes. The subcortical white matter of this brain showed 7.4% swelling, but without change in the electrolytes. Another brain showed tremendous swelling (36.6%) in the affected sylvian cortex with marked increase in tissue sodium (92 μEq per gram fresh weight) and decrease in tissue potassium (38 μEq per gram fresh weight). This tissue was apparently necrotic.
The putamen of this brain showed 18.2% swelling with increase in tissue sodium, 66 μEq per gram of fresh tissue, and decrease in tissue potassium content, 65 μEq per gram of fresh tissue. The subcortical white matter of the brain showed 4.3% swelling when the identical contralateral hemisphere was used as a control. However, the percentage dry weight value of the contralateral hemisphere of the brain was rather low, 30.31%, compared to the other. It is possible that in this case, with the tremendous amount of swelling in the gray matter, the edematous fluid may have crossed the corpus callosum into the opposite side, resulting in the low percentage dry weight value of the white matter of the contralateral hemisphere. When the percentage swelling was calculated with the mean control value of 32.45%, the subcortical white matter on the experimental side was equivalent to 7.1% swelling. However, no significant change in the electrolyte content was detected in the subcortical white matter.

Discussion

Despite the wide variety in the extent of the pathology among individual cases, ischemic cerebral swelling following sudden occlusion of a major cerebral artery can be a major cause of death in an acute phase or can result in greater morbidity in a chronic phase.1-2 Pathological studies based on animal experiments have demonstrated that with proximal MCA occlusion the extent of infarct was fairly uniform in the basal ganglia in the affected MCA territory, but that the lateral extension varied.3-9 In addition, the faulty microcirculation has been reported to be greater in the deep subcortical structures than in the cortex.9,10 However, little is known about the difference in effects of regional cerebral ischemia on the gray matter and white matter.3,9

In this study, percentage tissue dry weight and tissue sodium and potassium content were measured in the samples from the sylvian cortex, putamen and subcortical white matter in the affected MCA territory of monkeys with selective embolization of the ICA bifurcation to evaluate the different effects of ischemia on these structures. Edema developed in the putamen in two of three animals as early as after three hours of ischemia, but without detectable change in electrolytes. After four to five hours, ischemic cerebral swelling became obvious, particularly in the gray matter, in both the sylvian cortex and putamen in six of eight animals. Moreover, the gray matter samples from these structures, which showed 9.7% to 36.6% swelling, also exhibited 13% to 100% increase from the control value in sodium and 13% to 55% decrease from the control value in potassium content, except in one sample from the sylvian cortex after four hours of ischemia which showed 13.3% swelling but no significant change in electrolytes. Other gray matter samples which showed less than 12.6% swelling were not accompanied by significant changes in electrolytes. This tendency became clearer when the changes in tissue electrolytes were expressed as tissue sodium to potassium ratio (fig. 2). There was a statistical difference between the samples which showed less than 10% swelling without significant change in electrolytes and those which showed more than 10% swelling with a definite shift of tissue electrolyte content (p < 0.01). On the other hand, tissue swelling in the subcortical white matter, if present at all, was minimal (3.9% to 7.4% swelling) without detectable change in electrolytes and was accompanied by a much greater amount of edema (> two to seven times) in the gray matter of the same brain section. Figure 1 shows a coronal section of the brain which was exposed to four hours of ischemia. Hemispheric swelling is apparent on the experimental side. Moreover, ischemic changes in the gray matter structures of the affected side, particularly in the sylvian cortex, insula, striatum and amygdala, are much more marked than those of the subcortical white matter in the same affected MCA territory. The planimetric surface area of the gray matter of this specimen (the sylvian cortex,
insula and putamen) is 17% more on the affected side than that on the opposite side. Changes in the surface area of the subcortical white matter are minimal. From this evidence, it is clear that ischemic swelling of the gray matter plays a major role in the development of hemispheric swelling within hours of regional cerebral ischemia.

Questions have been asked, however, whether or not the swollen tissue produced by ischemia-hypoxia is entirely an accompaniment of tissue necrosis or an edematous state which possibly may be reversed. Studies on microcirculation and morphological changes in the ischemic brain after experimental occlusion of the MCA have shown that faulty microcirculation and tissue alteration at the molecular level developed after three to six hours of ischemia, admitting that the pathological process might not diffusely involve the entire area of ischemia which was normally supplied by the occluded artery. On the other hand, the “blood-brain barrier,” tested by extravasation of blood-borne protein tracers, has been reported to remain intact for many hours as well as the preservation of the “tight endothelial junction” of the capillary observed by electron microscopy.

According to Cammermeyer, the “physiological” perfusion fixation of the pathological specimen is needed to avoid postmortem artifact, which produced a limitation on carrying out an exhaustive morphological study in addition to the chemical analysis in this study. However, light microscopy of a specimen obtained from one of the brains, which showed more than 10% swelling of the gray matter and a definite change of tissue sodium and potassium content, showed a state of irreversible cell damage equivalent to those findings obtained with the meticulous preparation by other investigators (figs. 3A and B). In our preliminary study, we saw no abnormal staining of the swollen tissue with vital dyes such as Evans blue or fluorescein for at least up to five hours of regional cerebral ischemia.

From these results, it may be speculated that the swollen tissue (gray matter) which showed more than 10% swelling might be composed mostly of necrotic tissue and accordingly be accompanied by marked shift of sodium and potassium content between the intravascular CSF and cerebral tissue compartments. However, the tissue which showed less than 10% swelling without detectable change in the electrolytes might be a state of cerebral edema which might possibly be reversed. These results also may support the previous observation by other investigators using different methods that the early shift of water in the very early phase (within hours) of developing cerebral edema produced by a sudden occlusion of the MCA in animals might be caused by simple diffusion of water through the dysfunctional capillary wall or cell membrane with or without a permeability gradient between the intravascular CSF and cerebral tissue compartments. Moreover, this early edema appeared to develop primarily in the ischemic gray matter and later evolve into the ischemic vasogenic edema of the adjacent subcortical white matter with the development of tissue necrosis in the former structure.

Acknowledgment

The authors wish to thank Mr. D. Buchheit, Mr. J. Griffis, Mr. A. Kirisits, and Mr. G. Krawitz for technical assistance.

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O Watanabe, C R West and A Bremer

*Stroke*. 1977;8:71-76
doi: 10.1161/01.STR.8.1.71

*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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