Reperfusion After Cerebral Ischemia: Influence of Duration of Ischemia

NICHOLAS V. TODD, F.R.C.S., PIERO PICOZZI, M.D., H. ALAN CROCKARD, F.R.C.S., AND RALPH ROSS RUSSELL, M.D., F.R.C.P.

SUMMARY The influence of the duration of ischemia on the pattern of cerebral blood flow in recirculation was studied in anesthetised rats. Severe incomplete cerebral ischemia (mean ischemic flow = 5.8 ± 0.4 ml/100 g/min) was produced by four-vessel occlusion and recirculation permitted after 15, 30 or 60 minutes ischemia. All three groups showed an immediate hyperemia followed by hypoperfusion. Hyperemia was maximal following 15 minutes ischemia and least pronounced following 60 minutes ischemia (p = 0.0249). Hypoperfusion started most quickly following 15 minutes ischemia and was delayed following 60 minutes ischemia (p < 0.001). In established hypoperfusion there was no difference in flow between the three groups. The possible mechanisms of these changes in flow are discussed.

Stroke Vol 17, No 3, 1986

Recirculation after cerebral ischemia is a common clinical event. It occurs after the spontaneous break-up of cerebral emboli and follows the removal of clips used for temporary hemostasis during surgery for aneurysm and arteriovenous malformation. Operations such as extracranial-intracranial bypass are designed to increase circulation to chronically ischemic brain.

The initial period of recirculation after ischemia is of paramount importance and two patterns of post-ischemic circulatory disturbance have been described, the 'no-reflow phenomenon' and 'hyperemia-hypoperfusion'. The no-reflow phenomenon was originally demonstrated as an absence of carbon black staining after 5–7 minutes global cerebral ischemia in rabbits\(^1\) and has also been demonstrated in primates\(^2\) and rats.\(^3\) No-reflow can be reversed or prevented by recirculation at a satisfactory blood pressure, even if ischemia is prolonged.\(^4,5\) Explanations for the no-reflow phenomenon have included blockage of the vascular lumen by platelets or red cell aggregates;\(^6,7\) change in blood viscosity;\(^8\) local intravascular coagulation;\(^9\) and direct capillary compression from edematous endothelial and glial cells.\(^10–12\) The alternative pattern of post-ischemic circulatory disturbance is where an initial increase in cerebral blood flow, 'reactive hyperemia', is followed by a reduction in flow, 'delayed hypoperfusion'. This secondary hypoperfusion has been demonstrated in the isolated canine brain;\(^13\) following global cerebral ischemia in the cat,\(^14\) dog,\(^15\) monkey\(^16\) and rat\(^17\) and following focal cerebral ischemia in the cat.\(^18\)

It has been difficult to reconcile these two post-ischemic circulatory changes. Recent work has suggested that the no-reflow phenomenon will follow complete cessation of cerebral blood flow and does not occur if there is any residual flow, however small.\(^19,20\) Delayed hypoperfusion, by contrast, may follow both complete and incomplete cerebral ischemia.\(^19,20\)

It is important to define the factors in ischemia that influence post-ischemic circulatory changes. In these studies, we have chosen to vary the duration of ischemia with a fixed ischemic flow in order to decide whether post-ischemic hyperemia and hypoperfusion are universal phenomena or whether the degree and duration of these events are influenced by the duration of the preceding ischemia.

Methods

Animal Preparation

Experiments were performed in a standard manner by one person (N.V.T.) using a Zeiss operating microscope. Adult, male, Sprague-Dawley rats (200–300 g) were allowed free access to food and water pre-operatively and were premedicated with atropine 60 μg s.c. After induction of anesthesia with approximately 2% halothane, animals were paralyzed (2 mg/kg d-tubocurarine i.p.) and ventilated via a tracheostomy with 70% nitrous oxide, 30% oxygen and 1.5% halothane delivered by a small animal ventilator (Harvard 683). The carotid arteries were isolated from the vagus nerve and jugular vein to facilitate subsequent clipping. The left femoral vein and left and right femoral arteries were cannulated with polyethylene catheters (PE50).

Asthyan electrode was placed subcutaneously in the back. The carotid arteries were isolated from the vagus nerve and the closed cranial cavity. A silver/silver-chloride reference electrode was placed on each side using micro-manipulators. The electrodes were cemented into place using cold-setting methylmethacrylate cement which also re-established the closed cranial cavity. A silver/silver-chloride reference electrode was placed subcutaneously in the back. Following surgery, the animal was placed in lateral decubitus and the halothane concentration reduced to 0.5%.

Systemic blood pressure was measured continuous-
ly with a Statham P50 transducer and recorded on a Lectromed chart recorder. Arterial blood was sampled anaerobically in microhematocrit tubes (0.1 ml) and PaCO₂, PaO₂ and pH were measured on a blood gas analyser (ABL30 Radiometer, Copenhagen). pH was corrected where necessary by i.v. infusion of bicarbonate. Body temperature was maintained at 36.5 to 37.5°C by external warming. The hematocrit was measured at the end of the experiment.

With the vertebral arteries divided, cerebral ischemia was produced by bilateral carotid artery occlusion using Scoville-Lewis aneurysm clips. Removal of the carotid clips permitted recirculation.

rCBF

Six Teflon-coated platinum electrode (75 μ diam.) were placed into specific cortical regions stereotactically as described above and polarised at +400 mV to the reference electrode. CBF was measured by clearance of hydrogen (approximately 4% hydrogen in the inspired gas mixture), and the flow calculated by the initial slope technique between 30 and 90 seconds.

Experimental Protocol (table 1)

A total of 48 animals were used. The study measured rCBF, brain edema and blood-brain barrier (BBB) permeability in each animal. Brain edema and BBB permeability measurements required sacrifice of the animal and the results are reported in the accompanying paper. Animals were divided into three experimental groups:

<table>
<thead>
<tr>
<th>Group</th>
<th>Ischemia</th>
<th>Recirculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15 mins</td>
<td>n = 16</td>
</tr>
<tr>
<td>B</td>
<td>30 mins</td>
<td>n = 16</td>
</tr>
<tr>
<td>C</td>
<td>60 mins</td>
<td>n = 16</td>
</tr>
</tbody>
</table>

All animals were allowed to stabilise for 60 minutes after surgery. Anesthesia was maintained at a constant level (70% nitrous oxide, 30% oxygen, 0.5% halothane). rCBF was measured before ischemia, throughout ischemia and in recirculation at 5, 15, 30, 60, 120 and 180 minutes (or until sacrifice, if sooner). PaCO₂, pH and PaO₂ were measured before each flow.

Statistical Analysis

The flow data were compared by analysis of variance, using the BMDP program package. Data reduction and analysis were performed on the University of London CDC6600 computer.

Seven variables were used (Group + 6 electrodes, for each animal). The electrode data were transformed to give mean regional data.

At specified times in recirculation the design dependants were 3 x 3 (frontal, parietal, occipital x Groups A, B, C). The differences between the dependants means were compared to an error term. The degrees of freedom were calculated for independent cases (i.e., for animals, rather than electrodes).

Results

Three groups of animals were compared. The three groups were each of 16 animals made ischemic for either 15, 30 or 60 minutes. In all groups ischemia was followed by three hours reperfusion.

General Physiological Parameters (table 2)

Systemic arterial pressure PaCO₂, PaO₂ and systemic pH remained stable throughout the experiment. Four-vessel occlusion did not lead to systemic metabolic upset. On recirculation there was a slight reduction in systemic pH greater following 60 minutes ischemia. This was corrected by i.v. infusion of bicarbonate and never required more than 1–2 mmol of bicarbonate to return the systemic pH to normal limits. Whole blood hematocrit lay between 0.45–0.40.

Cerebral Blood Flow (table 3)

Halothane concentration was maintained at 0.5% at all times. There were differences in the pre-ischemic CBF regionally (table 3). Mean cortical CBF before ischemia was not significantly different between the three experimental groups.

Forty-eight rats underwent four-vessel occlusion and they all became ischemic. The hydrogen clearance curve showed an equilibration phase in the first 45 seconds after carotid clipping and then settled to a steady ischemic clearance which was maintained until the clips were removed. The mean ischemic flow was 5.8 ± 0.4 mls/100 g/min (mean all cortical regions ± S.E.M.). There were no significant differences between the levels of flow regionally or between the three experimental groups.

Removal of the carotid clips permitted reperfusion and there was a similar pattern of reflow in all cortical regions and in the three experimental groups (fig. 1). There was an immediate increase in rCBF. After a variable period of time this hyperemia was succeeded by ‘delayed hypoperfusion’ with flows reduced below control values. There were differences between the
three experimental groups in each of these phases of recirculation, and we have considered the data under the headings 1) no-reflow, 2) hyperemia, 3) duration of hyperemia and 4) hypoperfusion.

**No-Reflow**

On removal of the carotid clips there was an immediate clearance of any hydrogen still present in the brain. The first flow was measured at 5 minutes of recirculation and from a total of 210 electrodes in 36 rats, not one electrode failed to show reflow. Some brain regions failed to mount a typical hyperemia and this was related to the duration of the preceding ischemia. After 15 minutes ischemia, only 2.5% of electrodes showed flows lower than their pre-ischemic value. This increased to 11.7% after 30 minutes ischemia and to 15.7% after 60 minutes ischemia. Those regions that did not show post-ischemic hyperemia nevertheless followed a similar pattern of later reflow with a reduction in CBF until during hypoperfusion they were not separate from the group as a whole.

**Hyperemia (fig. 2)**

All brain regions and all three experimental groups showed post-ischemic hyperemia, defined as mean flows in recirculation significantly greater than pre-ischemic values. This hyperemia was always maximal immediately on recirculation (measured at 5 minutes) and it developed in the presence of a normal systemic blood-pressure (mean = 124 mmHg). The data are shown in table 3. There were 35 degrees of freedom. There was a significant group effect (F = 4.16; p = 0.0249) with peak hyperemia being greatest in Group A, least in Group C. There was also a site effect (F = 13.49; p < 0.001) with occipital flows being significantly reduced, compared to the frontal and parietal flow. The.

### Table 2: General Physiological Parameters

<table>
<thead>
<tr>
<th>Duration of ischemia</th>
<th>SAP (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>PaO₂ (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>124 ± 3</td>
<td>38.9 ± 0.7</td>
<td>171 ± 18</td>
<td>7.374 ± 0.005</td>
</tr>
<tr>
<td>30 mins</td>
<td>121 ± 2</td>
<td>37.7 ± 0.7</td>
<td>158 ± 14</td>
<td>7.356 ± 0.010</td>
</tr>
<tr>
<td>60 mins</td>
<td>127 ± 3</td>
<td>40.8 ± 0.7</td>
<td>192 ± 20</td>
<td>7.380 ± 0.012</td>
</tr>
<tr>
<td>Ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>120 ± 4</td>
<td>39.7 ± 0.6</td>
<td>161 ± 11</td>
<td>7.377 ± 0.016</td>
</tr>
<tr>
<td>30 mins</td>
<td>117 ± 3</td>
<td>38.5 ± 0.5</td>
<td>150 ± 7</td>
<td>7.367 ± 0.014</td>
</tr>
<tr>
<td>60 mins</td>
<td>126 ± 5</td>
<td>39.3 ± 0.4</td>
<td>175 ± 19</td>
<td>7.353 ± 0.017</td>
</tr>
<tr>
<td>5 mins reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>124 ± 3</td>
<td>42.2 ± 1.2</td>
<td>150 ± 7</td>
<td>7.343 ± 0.012</td>
</tr>
<tr>
<td>30 mins</td>
<td>123 ± 2</td>
<td>38.8 ± 1.0</td>
<td>142 ± 10</td>
<td>7.389 ± 0.021</td>
</tr>
<tr>
<td>60 mins</td>
<td>126 ± 4</td>
<td>41.0 ± 0.8</td>
<td>176 ± 22</td>
<td>7.390 ± 0.021</td>
</tr>
<tr>
<td>60 mins reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>126 ± 4</td>
<td>38.4 ± 1.1</td>
<td>149 ± 13</td>
<td>7.386 ± 0.010</td>
</tr>
<tr>
<td>30 mins</td>
<td>121 ± 2</td>
<td>39.2 ± 1.0</td>
<td>137 ± 8</td>
<td>7.388 ± 0.021</td>
</tr>
<tr>
<td>60 mins</td>
<td>132 ± 4</td>
<td>39.7 ± 1.0</td>
<td>161 ± 23</td>
<td>7.351 ± 0.029</td>
</tr>
<tr>
<td>180 mins reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>116 ± 3</td>
<td>38.0 ± 0.8</td>
<td>156 ± 15</td>
<td>7.392 ± 0.007</td>
</tr>
<tr>
<td>30 mins</td>
<td>120 ± 2</td>
<td>40.6 ± 1.5</td>
<td>136 ± 12</td>
<td>7.354 ± 0.017</td>
</tr>
<tr>
<td>60 mins</td>
<td>130 ± 3</td>
<td>38.7 ± 1.1</td>
<td>179 ± 18</td>
<td>7.344 ± 0.017</td>
</tr>
</tbody>
</table>

SAP = systemic arterial blood pressure.
Values = mean ± SEM.

### Table 3: Post-Ischemic Cerebral Blood Flow — Rat Cortex

<table>
<thead>
<tr>
<th>Ischemic Time</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>30 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Pre-Ischemia</td>
<td>80 ± 5</td>
<td>93 ± 9</td>
<td>96 ± 9</td>
</tr>
<tr>
<td>Ischemia</td>
<td>5.5 ± 0.4</td>
<td>6.3 ± 0.9</td>
<td>5.8 ± 0.5</td>
</tr>
<tr>
<td>5 min</td>
<td>205 ± 10</td>
<td>173 ± 19</td>
<td>162 ± 15</td>
</tr>
<tr>
<td>15 min</td>
<td>86 ± 10</td>
<td>117 ± 13</td>
<td>162 ± 21</td>
</tr>
<tr>
<td>30 min</td>
<td>49 ± 5</td>
<td>56 ± 5</td>
<td>119 ± 14</td>
</tr>
<tr>
<td>60 min</td>
<td>44 ± 4</td>
<td>48 ± 4</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>2 hrs</td>
<td>54 ± 6</td>
<td>60 ± 5</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>3 hrs</td>
<td>46 ± 2</td>
<td>63 ± 6</td>
<td>55 ± 7</td>
</tr>
</tbody>
</table>

CBF ml/100 g/min in 3 cortical regions.
Flows were measured at rest, during ischemia and during reperfusion (5, 15, 30, 60 min and 2, 3 hrs). Three experimental groups with ischemic times of 15, 30, 60 min followed by reperfusion.
Results are mean ± SEM.
For statistical analysis refer to text.
FIGURE 1. CBF following cerebral ischemia. Pre-ischemic flow was $94 \pm 8 \text{ mls/100 g/min}$ (there was no significant difference between the three experimental groups). During ischemia, flow was reduced to $5.8 \pm 0.4 \text{ mls/100 g/min}$. On reperfusion, there was an immediate hyperemia followed by delayed hypoperfusion in all groups. $a$ — 15 minutes ischemia, $b$ — 30 minutes ischemia, $c$ — 60 minutes ischemia. $a$ — all flows significantly greater than pre-ischemic flows, 'hyperemia', $p < 0.01$, $b$ — all flows significantly lower than pre-ischemic flow, 'hypoperfusion', $p < 0.01$.

Group and site effects were independent (site/group interaction, $F = 1.35; p = 0.261$).

Duration of Hyperemia (fig. 3)

There was not an abrupt change from hyperemia to hypoperfusion and we calculated the time for the hyperemic flow to reach control values for each electrode. There was no regional difference, so the regional data were summed to give a mean cortical value for each animal. The duration of hyperemia in the three groups was $A = 16.9 \pm 0.5 \text{ mins}$; $B = 21.9 \pm 1.3 \text{ mins}$; $C = 62.1 \pm 7.4 \text{ mins}$ (results = mean ± S.E.M.). Differences between the means were compared using one-way ANOVA ($p < 0.001$) and we concluded that longer ischemia prolonged post-ischemic hyperemia.

Delayed Hypoperfusion (fig. 4)

All three experimental groups and all brain regions showed hypoperfusion, i.e., a reduction in CBF to levels significantly lower than pre-ischemic values (table 3). There was a difference in the rate of onset of hypoperfusion as described above. During established hypoperfusion (at two and three hours recirculation) differences between design dependants, brain region

FIGURE 2. Hyperemia following cerebral ischemia. All flows were significantly greater than the pre-ischemic flow in the same group. The peak of hyperemia was reduced following a longer duration of ischemia. $A$ — 15 minutes ischemia, $B$ — 30 minutes ischemia, $C$ — 60 minutes ischemia. $a$ — pre-ischemic flow, $b$ — flow at 5 minutes reperfusion. Results are mean cortical CBF ml/100 g/min with standard error bars. $a$ — significantly greater than pre-ischemic flow, $p < 0.01$. $*$ significant group difference, $p = 0.0249$.

FIGURE 3. Duration of post-ischemic hyperemia. The duration of hyperemia was calculated for each electrode and taken as the time in reperfusion that each flow was raised above its own pre-ischemic value. $A$ — 15 minutes ischemia, $B$ — 30 minutes ischemia, $C$ — 60 minutes ischemia. Results are group means with standard error bars. $*$ significant difference between the three groups, $p < 0.001$.

FIGURE 4. Hypoperfusion following cerebral ischemia. CBF at 120 minutes reperfusion after cerebral ischemia. All three groups showed a significant reduction in flow 'hypoperfusion'. There was no difference in flow between the three experimental groups. $A$ — 15 minutes ischemia, $B$ — 30 minutes ischemia, $C$ — 60 minutes ischemia. $a$ — pre-ischemic flow, $b$ — flow at 120 minutes reperfusion. Results are mean cortical CBF ml/100 g/min with standard error bars. $*$ — significantly lower than pre-ischemic flow, $p < 0.01$. 
probably reflects a difference in effective arterial cortex despite the same degree of ischemia, and this maximal vasodilatation. Flow was lower in the occipital groups was striking and this may represent a state of this dilated vascular bed, and it might be expected that by direct observation. Hyperemia represents flow in the frontal and parietal cortices within each region. During ischemia, powerful vasodilator substances such as adenosine, K+, H+ and CO2 accumulate and dilution of pial vessels has been confirmed by direct observation. Hyperemia represents flow in this dilated vascular bed, and it might be expected that there would be a maximal vasodilatation with even short periods of cerebral ischemia. The similarity of flow in the frontal and parietal cortices within each group was striking and this may represent a state of maximal vasodilatation. Flow was lower in the occipital cortex despite the same degree of ischemia, and this probably reflects a difference in effective arterial blood-pressure. In the four-vessel occlusion model, all cortical regions reperfuse from the carotid arteries and the occipital cortex is furthest from the ‘head’ of pressure. If this explanation is correct, it suggests that manipulation of the blood pressure in early recirculation may be a method of increasing or decreasing hyperemia. There were differences in the degree of hyperemia between the three experimental groups with Group A showing the fastest flow and Group C the slowest. If we assume maximal vasodilatation in all groups, then this difference in flow must be due to a difference in perfusion pressure (= systemic arterial pressure — intracranial pressure). Since arterial blood-pressure was the same, variations in perfusion pressure are probably accounted for by changes in intracranial pressure (ICP) which is associated with brain edema. We found the amount of edema to be greater with increasing duration of ischemia and this probably accounts for the reduction in post-ischemic hyperemia in Groups B & C.

We would therefore suggest that following incomplete ischemia, immediate hyperemia is the rule and that this is a consequence of maximal vasodilatation. Differences in hyperemic flow represent changes in perfusion pressure, either a change in systemic blood-pressure or ICP. After longer ischemia, the duration of hyperemia was prolonged. Metabolic vasodilator products produced during ischemia lead to post-ischemic vasodilatation. With prolonged ischemia, the volume of these products is greater and also the cellular mechanism necessary for their metabolism and/or excretion are probably damaged to a greater extent. It is therefore likely that the prolongation of hyperemia following longer ischemia is secondary to reduced clearance of vaso-active products.

We have shown that hypoperfusion started significantly sooner after short periods of ischemia. Although it is difficult to compare results from different species and different experimental methods, previous work tends to confirm this. Hypoperfusion starts about 15 to 20 minutes after five minutes global ischemia in the dog; 40 minutes after 30 minutes global ischemia in the cat and about 80 minutes after 60 minutes global ischemia in the cat. Hypoperfusion occurred in our experiments despite maintenance of a normal systemic blood-pressure and PaCO2, and must be due to an increase in vascular resistance. This may be caused by (I) intravascular, (II) extravascular, or (III) vascular factors.

Although intravascular stasis, (I), is important in the no-reflow phenomenon, it is difficult to postulate spontaneous sludging occurring after hyperemia, and thrombi cannot be demonstrated in the cerebral vessels after 30 minutes incomplete ischemia in the rat. ‘Intracerebral squeeze’ (II) or vascular compression from brain swelling is a potential mechanism of post-ischemic hypoperfusion. However, the changes in flow do not follow the known changes in brain water, and CBF is most consistently reduced at 1–4 hours of reperfusion at a time when brain water is resolving. We could not correlate reduced post-ischemic CBF...
with brain edema. Hypoperfusion occurred soonest (Group A) where brain edema was least and was delayed (Group C) where brain edema was maximal. Equally at two hours recirculation, all groups showed the same hypoperfusion despite marked differences in brain edema. A more likely explanation is that these post-ischemic flow changes occur because of a recovery of vascular smooth muscle tone. This recovery occurred most quickly after short periods of ischemia (Group A) and was delayed following longer periods of ischemia (Group C). In contrast, when hypoperfusion is established, flow was reduced to 60–70% of control values in all cortical regions and was independent of the duration of the preceding ischemia.

What are the consequences of these post-ischemic circulatory disturbances? During severe ischemia, there is a rapid failure of cellular metabolism with accumulation of ADP, a drop in pH and ionic fluxes (K⁺, Na⁺, Ca²⁺) across the cellular membrane. On recirculation, there is an increase in oxygen and glucose availability and a gradual reversal of the pathological changes. Various workers have suggested that hyperemia is an important pre-requisite of return of cerebral function. Others have emphasized its potentially harmful effect. Clearly, 'no-reflow' implies continuation of cerebral ischemia and hyperemia demonstrates patency of the vascular bed. However, the cerebral metabolic rate (CMR) is reduced in early recirculation and very fast flows are inappropriate to the metabolic needs. It would therefore appear that CBF and CMR are uncoupled in early recirculation.

The mechanism and consequences of post-ischemic hyperemia are not clear. The reduction in CBF may simply reflect a reduced CMR and this would imply CBF/CMR coupling during hypoperfusion. Some workers have shown a steady rise in post-ischemic CMR and it may be that CBF and CMR remain uncoupled in later recirculation. We did not measure CMR, we feel that CMR is unlikely to have been the same in our experimental groups. We found no difference in CBF between the three groups and we would suggest that CBF and CMR remain uncoupled during the phase of hypoperfusion. Further work is required to clarify this point and also to determine the mechanisms of post-ischemic hyperemia.

In conclusion, after incomplete cerebral ischemia there is an immediate hyperemia followed by hypoperfusion and these flow changes may reflect changes in vascular smooth muscle tone. Hyperemia is a consequence of reperfusion into a maximally vasodilated bed and is reduced following longer periods of ischemia where the ICP is raised. Hypoperfusion starts most quickly after the shortest period of ischemia and this may be due to a return of vascular tone. In established hyperperfusion, flow is 60 to 70% of control values, regardless of the duration of the preceding ischemia.

Acknowledgments
The authors are grateful for the technical help of Miss Kathryn Allen and Miss Caroline Williams, and to Miss Bridie McAteer for secretarial assistance.

References
BRAIN SWELLING due to water accumulation is an important complication of cerebral ischemia and will frequently lead to trans-tentorial herniation and death. The amount of water accumulating during ischemia depends on the level of flow during ischemia and its duration, and on whether the ischemia is complete or incomplete. Restoration of blood flow to ischemic brain may improve outcome and operations to revascularize the ischemic brain have been devised. Unfortunately reperfusion may lead to an increase in brain water, occurring either immediately or later, when it is associated with breakdown of the blood-brain barrier. We have used the model of cerebral ischemia described earlier to measure cerebral blood flow (CBF), brain edema and blood-brain barrier (BBB) permeability quantitatively and on a regional basis in the same animal. This study examined the effect of increasing the duration of ischemia on the development and resolution of post-ischemic brain edema.

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Duration of Ischemia Influences the Development and Resolution of Ischemic Brain Edema

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This work was supported by the Medical Research Council of Britain and Action Research for the Crippled Child. N. V. Todd was awarded the MCR Training Fellowship in Neurosurgery. P. Piccitti was a British Council Fellow from the First University Hospital, Naples, Department of Neurosurgery.

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Received January 22, 1985; revision #1 accepted November 5, 1985.
Reperfusion after cerebral ischemia: influence of duration of ischemia.
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Stroke. 1986;17:460-466
doi: 10.1161/01.STR.17.3.460

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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