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This Week's Citation Classic

Ames A, III, Wright R L, Kowada M, Thurston J M & Majno G. Cerebral ischemia. II. The no-reflow phenomenon. *Amer. J. Pathol.* **52:**437-53, 1968.
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After seven minutes of circulatory arrest, it became increasingly difficult to fill rabbits' cerebral vessels with a carbon black suspension or to wash out the blood with Ringer's solution. If the blood had been displaced prior to the arrest, reperfusion with carbon black was complete. [The *SCI*® indicates that this paper has been cited over 320 times since 1968.]

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"This study was a novel experience for me. Experiments designed to test a rather adventurous hypothesis provided support for each aspect of it —or so it appeared.

"We had previously found, to our surprise, that central nervous tissue maintained *in vitro* could recover from 20 minutes of ischemia, and we were trying to reconcile this observation with conventional wisdom that brain *in situ* is severely damaged after seven minutes of circulatory arrest. An important difference between the two situations is the dependence of the brain *in situ* on resumption of blood flow. There might be some difficulty, we postulated, on reestablishing flow. If ischemia stopped the active transport of Na + out of the cells, they would swell with fluid from the interstitial spaces and capillaries until the latter became too narrow to permit passage of the formed elements in the blood. At this point the situation would become irreversible, though the cells themselves were still viable. That was the hypothesis.

"Reversible ischemia was produced by the neurosurgical skills of Wright and Kowada, and the brains were examined in the pathology laboratories of Majno and Thurston. The experiments demonstrated an impairment of reperfusion following stasis that was not prevented by anticoagulants. Separate studies showed swelling of perivascular cells, with luminal narrowing, and protection by osmotic agents added to the blood. Q.E.D. (we thought).

"Experiments we have performed since then have confirmed the difficulty with reperfusion, but have not confirmed the mechanism proposed for it. There is now good evidence that the main problem is a progressive increase in the viscosity of the immobilized blood, compounded by a loss of auto-regulation and neurogenic hypotension.[1] Osmotic agents protect by lowering blood viscosity rather than by preventing cell swelling, which is not marked until later. So it is now apparent that our original hypothesis only partially survived experimentation.

"The paper received little attention at first. Few laboratories were studying ischemia at that time. There was an aura of inevitability about ischemic cell death that discouraged investigation. But with the concept that survival may be determined by factors that can be defined and perhaps controlled there has been a rapidly increasing interest in the subject. I believe our paper has contributed to this.

"Studies of reperfusion following ischemia have now been reported by many investigators working with a variety of tissues. The phrase 'no-reflow phenomenon' has come into rather common usage, which is flattering but also unfortunate since it is now evident that the all-or-none connotation is inappropriate. The circumstances under which impaired reperfusion contributes to cell death from ischemia have not been fully defined and remain the subject of a healthy controversy."

1. Fischer E G, Ames A, III & Lorenzo A V. Cerebral blood flow immediately following brief circulatory arrest. *Stroke* **10:**423-7, 1979.