

Plum F, Posner J B & Troy B. Cerebral metabolic and circulatory responses to induced convulsions in animals. *Arch. Neurol.* 18:1-13, 1968.

[Department of Neurology, Cornell University Medical College, New York, NY]

We used metrazol or electric shock to produce generalized cerebral seizures in lightly anesthetized dogs and monkeys. Paralysis and ventilation eliminated artifacts of convulsive movement and hypoxemia. Brain oxidative metabolism increased up to five times, but cerebral blood flow rose even more, so that substrate supply equaled or exceeded metabolic demand [The *SCI*® indicates that this paper has been cited in over 180 publications since 1968.]

Fred Plum

Department of Neurology
New York Hospital-Cornell Medical Center
New York, NY 10021

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When Jerry Posner and I started these experiments with Bart Troy, a research fellow, we were seeking, among other things, the physiological couple that linked appropriate alterations in cerebral blood flow to changes in brain metabolism. (Despite the efforts of many investigators, that quest remains largely unfulfilled.) We also realized that little was known about the brain's general metabolic function during epileptic attacks, especially because previous studies had not clearly separated the systemic effects of muscular convulsions and hypoxemia from the chemical events that independently affected the brain. Looking back, it is astonishing how limited the information was. No quantitative index existed about how much work the brain performed to generate a seizure, and at least one theory proposed that the reason that seizures stopped was that they exhausted the brain's oxygen content.

Although the technical limitations of our instruments permitted only semiquantitative conclusions, the experimental findings showed that the brain possesses an extraordinary capacity to increase its oxidative me-

tabolism in the presence of intense stimulation. Furthermore, thanks to systemic hypertension neurogenically mediated as a by-product of the seizures and a simultaneous relaxation of cerebral resistance vessels, the epileptic brain increased its blood supply even more than its metabolic demand during an attack. As a result, cerebral venous oxygen content actually increased, although this oversupply appeared to affect neither the duration of the attack nor the period of metabolic depression that inevitably followed it. A notable physiologic change was that during the intense cerebral stimulation, tissue CO_2 production somewhat exceeded oxygen consumption, presumably reflecting titration of bicarbonate by increased lactate, as found in later studies. This nonhypoxic redox shift, indicating increased reduction of the tissue NADH/NAD^+ ratio during stimulation, has been confirmed repeatedly by direct analysis of metabolic intermediates. The change appears to reflect inherent differences in the rates at which cytoplasmic glycolysis and mitochondrial respiration in the brain respond to stimulation. What biologic advantage it serves remains unclarified.¹

Partly, I suppose, because of the dramatic and at least somewhat unexpected nature of the results, the above experiments have been followed by many related ones in our own and other laboratories. These have been conducted in both experimental animals and most recently in humans by the techniques of positron emission tomography, which can quantify local cerebral flow and metabolism in health and disease. The studies have provided more wide-ranging, precise, fundamental, and therapeutic information about the metabolism of epilepsy than could have been anticipated 18 years ago. The reports of Collins, Meldrum, Duffy, Siesjo, Engle, and their collaborators deserve special mention in this respect and are cited along with many others in an excellent recent review by A.G. Chapman.²

- 1 Plum F, Duffy T E & Collins R C. Cerebral oxygen and glucose metabolism during seizures (Jobsis F F, ed) *Oxygen and physiological function*. Dallas, TX Professional Information Library, 1976 p 480-90
- 2 Chapman A G. Cerebral energy metabolism and seizures (Pedley T A & Meldrum B S, eds) *Recent advances in epilepsy* #2 Edinburgh, Scotland Churchill-Livingstone, 1985 p 19-63