CC/NUMBER 17
APRIL 28, 1986

This Week's Citation Classic®

James I M, Millar R A & Purves M J. Observations on the extrinsic neural control of cerebral blood flow in the baboon. *Circ. Res.* 25:77-93, 1969.
[ARC Institute of Animal Physiology, Babraham, Cambridge, England]

The participation of cerebral vasomotor nerves in cerebral vascular responses to changes in blood gas tensions and arterial pressure was evaluated. The results indicated that cerebral blood vessels are under reflex control. [The *SCI*® indicates that this paper has been cited in over 235 publications.]

I.M. James
Royal Free Hospital
Hampstead, London NW3 2QG
England

October 23, 1985

In 1968 I had just completed my PhD at Cambridge University, England, where my supervisor was Ivor Mills. The work largely involved the measurement of cerebral blood flow in humans by the intra-arterial injection of xenon^{133}. During this period, I had worked quite closely with R.A. Millar, who was the principal neuroanaesthetist at the Cambridge Neurosurgical centre. Michael Purves, who was on the staff of the Department of Medicine, was an authority on chemo- and baroreceptors and had access to primate facilities at the Animal Research Council centre at Babraham.

In the 1960s it was generally held that the autonomic nervous system had little influence on the cerebral circulation. The fact that numerous investigations even then had demonstrated the presence of sympathetic and parasympathetic nerve terminals was frequently ignored. Whilst there was, on the surface of it, an appreciable literature denying any physiological role for the autonomic nervous system, most papers quote earlier papers that in turn quote even earlier papers. Certainly the problem had not recently been reinvestigated using modern radioisotope techniques. Ironically some of the best papers were those of Forbes and Wolff[1] and those of Chorobski and Penfield[2] dating back to the late 1920s and early 1930s.

The need for a good study using modern methodology became obvious almost simultaneously to all three of us. The only problem was one of time. I was due to move to the Royal Free Hospital in London within months, Purves was moving to the Department of Physiology in Bristol, and shortly afterward Millar was appointed to the Chair of Anaesthetics in Glasgow. The experiments recorded in our *Circulation Research* article were completed in a period of approximately eight weeks. This was the only time, in fact, that we ever had the opportunity to work together.

I believe one reason our paper has been so widely quoted is that we adopted a new approach to the problem, not just a new methodology. Virtually all experiments until that time had been directed at determining how far autonomic nerves affected cerebral vascular responses under normal conditions, i.e., normoxia, normocypnia, and normotension. We attempted instead to evaluate the participation of the cerebral vasomotor nerves in cerebral vascular responses to changes in blood gas tensions and arterial pressure.

Within physiological limits of blood gas tensions and arterial blood pressure, section of the cervical sympathetic nerve led to a consistent rise in cerebral blood flow of up to +14 percent of control, but this difference increased as P_aCO_2 was lowered and as mean arterial pressure was raised. Following sympathectomy, the relation between blood flow and mean arterial pressure altered so that flow was no longer independent of pressure. When the cervical sympathetic nerve was stimulated electrically, blood flow always diminished proportional to the resting level and to the level of P_aCO_2.

Qualitatively similar results were obtained when either the vagus and the depressor nerve or the depressor nerve alone were cut or stimulated. Section of the nerves gave rise to small and inconsistent changes in blood flow, but the vascular response to CO_2, low oxygen, and hypotension was markedly reduced. Stimulation of the central cut end of the vagi caused substantial increases in blood flow that were independent of the level of P_aCO_2. Some confirmatory evidence was obtained in this series of experiments that vasodilator fibres were carried in the facial nerve, but the results suggested that alternative apparent dilator pathways could exist.

Whilst it would be fair to say that the exact role of the autonomic nervous system in the control of the cerebral circulation is still a topic of continuing debate,[3-5] those experiments of 1968 showed that the function of the autonomic nerves contributes only slightly toward resting vascular tone but is of particular importance when blood gas tension or systemic pressure deviates from the physiological range.

1. **Forbes H S & Wolff H G.** Cerebral circulation. III. The vasomotor control of cerebral vessels. *Arch. Neurol. Psychiat.* 19:1057-86, 1928. (Cited 115 times since 1955.)
2. **Chorobski J & Penfield W.** Cerebral vasodilator nerves and their pathway from the medulla oblongata. With observations on the pial and intracerebral vascular plexus. *Arch. Neurol. Psychiat.* 28:1257-89, 1932. (Cited 180 times since 1955.)
3. **James I M.** Autonomic control of the cerebral circulation. (Meldrum B S & Marsden C D, eds.) *Primate models of neurological disorders.* New York: Raven Press, 1975. p. 167-80.
4. **James I M & MacDonell L A.** The role of baroreceptors and chemoreceptors in the regulation of the cerebral circulation. *Clin. Sci. Mol. Med.* 49:465-71, 1975. (Cited 35 times.)
5. **Kontos H A.** Regulation of cerebral circulation. *Annu. Rev. Physiol.* 43:397-407, 1981. (Cited 30 times.)