The data described in this article showed that angiotensin affects the central nervous system, resulting in increased arterial pressure and vascular resistance caused by sympathetic vasomotor discharge. The effect involves the area postrema, a fourth-ventricle circumventricular organ having a deficient blood-brain barrier. (The SCP indicates that this paper has been cited in over 250 publications.)

Almost concurrently, C.J. Dickinson had forwarded the hypothesis that essential hypertension results from relative ischemia of central vasomotor centers due to increased cerebrovascular resistance produced by activation of the renal pressor system. Attempts by Dickinson and McCubbin failed to show that Ang II infusion into the hindbrain circulation of the anesthetized dog produced pressor responses different from those obtained by intravenous infusion. However, I had the opportunity to talk with Dickinson at the 1967 Physiological Congress in Washington, DC. That discussion greatly influenced my research.

We concluded that the failure to observe a central effect of Ang II was possibly due to the CNS-depressing effect of pentobarbital. By repeating those experiments and measuring responses to vertebral artery Ang II infusions, using dogs equipped with electromagnetic flowmeters and anesthetized with morphine-chloralose, we showed that infusion of small doses of Ang II (without effect when given intravenously) into the vertebral arteries produced a pressor response. The dose-response curve suggested a neuronal effect, and additional experiments showed that the area postrema in the fourth ventricle was the angiotensin-sensitive structure mediating blood pressure increase via activation of central vasomotor sympathetic outflow.

I believe this paper is frequently cited because it provided the first comprehensive description of the direct action of Ang II on a brain structure highly sensitive to the hormone (area postrema), documented the mechanism of action, and proposed that the central effects of Ang II revealed a feedback link between the brain and the renal pressor system. (The fact that this controversial article was reviewed by seven referees foretold its future as an often-cited reference.)

Since 1972 we have affirmed area postrema involvement in the regulation of blood pressure and sympathetic nerve activity by many studies, including characterization of its anatomical and neurochemical substrate and the discovery that it functions in the tonic control of arterial pressure and the expression of the early phase of renovascular hypertension. For this latter work I received the 1979 Harry Goldblatt Award from the American Heart Association, Council of High Blood Pressure Research.