

Bunag R D, Page I H & McCubbin J W. Neural stimulation of release of renin.
Circ. Res. 19:851-8, 1966.
[Research Division, Cleveland Clinic Foundation, OH]

The release of renin from the kidney during nonhypotensive bleeding was shown to be mediated by the sympathetic nervous system. [The *SCI*[®] indicates that this paper has been cited in over 320 publications since 1966.]

Ruben D. Bunag
Department of Pharmacology,
Toxicology and Therapeutics
College of Health Sciences
and Hospital
University of Kansas
Kansas City, KS 66103

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In 1964 I joined the Cleveland Clinic in the Research Division then headed by Irvine H. Page to study various aspects of experimental hypertension. As a new postdoctoral research fellow, I was assigned to work with James McCubbin, who was interested in studying renin release from kidneys in anesthetized dogs. Another research fellow working with him previously had used hemorrhage to stimulate the kidneys to release more renin by lowering systemic blood pressure.

While trying to learn experimental procedures that were being used routinely in their laboratory, I noticed that the amounts of renin in blood sampled from the renal veins increased even in dogs that were bled so slightly that systemic arterial pressure remained unaltered. This was rather surprising because until then we had assumed that hemorrhage released renin by lowering blood pressure and thereby reducing renal perfusion pressure. The fact that renin release still increased even when blood pressure did not fall suggested that some other stimulus had been activated by bleeding. Following such logic, we proceeded to explore the possibility that the stimulus for renin release during nonhypotensive bleeding resulted from sympathetic nerve activation. And, indeed, we later found that the renal response to slow bleeding could be inhibited by blocking sympathetic pathways through either ganglioplegia with tetraethyl-

ammonium or local anesthesia of the renal nerves with lidocaine. Furthermore, we also found that as long as renal perfusion was kept constant, other procedures like carotid occlusion or intravenous infusions of adrenergic drugs could be used instead of hemorrhage to effectively stimulate the sympathetic nerves and to increase renin release.

On looking back, it is not easy to determine why that paper has been so widely cited. We were certainly not the first to think of sympathetic involvement. Even before our paper was published, others had already shown that renin release could be increased by either infusing catecholamines or stimulating the renal nerves electrically.¹ An important technical advantage may have been introduced fortuitously by our initial need to use nonhypotensive bleeding, because it made us recognize the importance of keeping renal perfusion pressure constant in order to demonstrate sympathetic mechanisms unequivocally. This difference allowed us to speculate concerning the role of renal nerves in the physiological regulation of renin release, and it also led us to select a meaningful title for the paper. By contrast, most preceding reports had titles that seemed more concerned with mentioning minute details rather than emphasizing their probable implications.

My most difficult obstacle came unexpectedly as we prepared to publish our results. Although Page and McCubbin were both very accomplished and competent writers, my own experience in scientific writing had been rather limited. Consequently, they had to teach me the rudiments through trial and error. They patiently guided me through 18 preliminary drafts, which underwent meticulous corrections and revisions that lasted for several agonizing months. Eventually, I was able to complete a manuscript for submission to *Circulation Research*, but despite all our efforts, the journal's editors asked for still further revisions before finally accepting it for publication. In retrospect, those efforts now seem worthwhile since our original observations on neural stimulation of renin release were confirmed almost immediately² and have been generally well accepted.^{3,4}

1. Vander A J. Effect of catecholamines and the renal nerves on renin secretion in anesthetized dogs. *Amer. J. Physiol.* 209:659-62, 1965. (Cited 500 times.)
2. Hodge R L, Lowe R D & Vane J R. Increased angiotensin formation in response to carotid occlusion in the dog. *Nature* 211:491-3, 1966. (Cited 70 times.)
3. Zanchetti A, Stella A, Leonetti G, Morganti A & Terzoli L. Control of renin release: a review of experimental evidence and clinical implications. *Amer. J. Cardiol.* 37:675-91, 1976. (Cited 85 times.)
4. Torretti J. Sympathetic control of renin release. *Annu. Rev. Pharmacol. Toxicol.* 22:167-92, 1982.