

Küchel O, Fishman L M, Liddle G W & Michelakis A. Effect of diazoxide on plasma renin activity in hypertensive patients. *Ann. Intern. Med.* 67:791-9; 1967. [Department of Medicine, Vanderbilt Univ. School of Medicine, Nashville, TN]

This paper contained the first observation that approximately one-third of patients with essential hypertension, although lacking primary aldosteronism, have a low plasma renin activity that doesn't respond to diazoxide-induced hypotension. They also have less tachycardia, prolonged hypotension, and more hyperglycemia than the remaining two-thirds. [The SC¹⁸ indicates that this paper has been cited in over 185 publications since 1967.]

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One can easily imagine the practical impact of the hypothesis of Jerome Conn that 20 percent of patients with so-called *essential hypertension* have an *unrecognized adrenal aldosteronoma* and could be cured by adrenal surgery.¹ I was both fascinated and incredulous: if true, a relatively easy measurement of plasma renin activity (PRA) by the method of Boucher² combined with aldosterone determination could recognize silent adrenal adenomas and mean a cure by surgery for one in five hypertensive patients! The problem was that the screening of these patients was an inconvenient and long procedure. They had to be admitted to a metabolic ward, get into sodium balance on a controlled sodium intake for aldosterone measurements, and afterwards be placed on a low-sodium diet and their PRA measured in response to sodium depletion and orthostatism.

This painstaking procedure prompted us at Vanderbilt University in Nashville to develop an alternative test that could detect PRA, suppression while requiring only a few hours of supervision of the patient. One possibility involved the use of rapidly acting loop diuretics such as furosemide. We were at this time, however, so obsessed by fear of a sudden potassium depletion in patients who tended to be hypokalemic anyway that we abandoned this challenge. Since reduction in renal perfusion pressure also stimulates PRA production, we opted for diazoxide, a rapidly acting hypotensive agent of short duration, as a PRA stimulant. After many methodological setbacks related to seasonal and delivery-dependent variations in the rat pressor assay, we eventually received a very good discrimination between PRA responders and nonresponders. Patients with low and unresponsive PRA were also found to have, in response to diazoxide, a prolonged hypotension; less tachycardia, and more hyperglycemia. It also became evident that suppression of PRA in the hypertensive population is far more common than is primary aldosteronism. The existence of a subcategory of essential hypertensive patients with suppressed PRA has thus been suggested.

The subgroup of low-renin hypertension received wide attention during the 1970s when Laragh advocated renin profiling of hypertensive patients with prognostic and therapeutic implications.³ Although renin profiling is not a generally accepted procedure, low and unresponsive PRA remains a valuable index of mineralocorticoid hypertension and sometimes also leads to the choice of therapy. The suppressed PRA appears to be a marker of volume-expanded essential hypertension of longer duration associated with abnormalities in the cellular sodium transport.⁴ This form of hypertension predominates in older and black patients.

In retrospect, the reason this article has been so frequently cited is that it identified for the first time the category of low-renin essential hypertension by demonstrating that low and unresponsive PRA is not necessarily a sign of primary aldosteronism. The irony of this study was that it made a positive observation departing from a hypothesis that proved to be wrong. This shows that a hypothesis stimulating further inquiry, even if unsupported by findings, is an essential element of progress.

1. Conn J W, Cohen E L, Rovner D R & Nesbitt R M. Normokalemic primary aldosteronism: a detectable cause of curable "essential" hypertension. *J. Amer. Med. Assn.* 193:200-6, 1965. (Cited 185 times.)
2. Boucher R, Veyrat R, de Champlain J & Genest J. New procedures for measurement of human plasma angiotensin and renin activity levels. *Can. Med. Assn. J.* 90:194-201, 1964. [See also: Boucher R. Citation Classic. *Current Contents* (2):13, 9 January 1978.]
3. Laragh J H. Vasoconstriction—volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *Amer. J. Med.* 55:261-74, 1973. (Cited 365 times.)
4. Haddy F J. Sodium-potassium pump in low-renin hypertension. *Ann. Intern. Med.* 98:781-4, 1983.