

# This Week's Citation Classic

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**Haber E, Koerner T, Page L B, Kliman B & Purnode A.** Application of a radio-immunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J. Clin. Endocrinol. Metab.* **29**:1349-55, 1969.  
[Harvard Med. Sch., and Cardiac Unit, Med. Serv., Mass. Gen Hosp.; Tufts Univ. Sch. Med., and Med. Serv., Newton-Wellesley Hosp., MA]

**A radioimmunoassay employing a highly specific antiserum to angiotensin I and its application to the determination of the plasma enzyme renin is described. Plasma renin activity was shown to vary in normal individuals with sodium intake, posture, and the administration of diuretics. The values of renin activity obtained by immunoassay of angiotensin I correspond closely to those observed by bioassay in similar metabolic studies but provide an advantage of relative simplicity, specificity, and reproducibility. [The SC<sup>®</sup> indicates that this paper has been cited over 1,165 times since 1969.]**

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"Renin, a plasma enzyme synthesized largely in the kidneys, is important in the regulation of blood pressure both in normal and diseased states. Clinical and physiologic investigations of the role of renin in vasomotor control had been impeded by the complexity and lack of general applicability of the bioassays then available. The genesis of my interest in renin was largely fortuitous. I was working on copolymers of several physiologic peptides and polyamino acids as model antigens. I was exploring the question of whether or not a simple antigenic stimulus would result in a less heterogeneous antibody response. Indeed, a far more restricted antibody response occurred with some of these peptides.<sup>1</sup> In a casual conversation in the dining room of the Massachusetts General Hospital with Lot B Page, then head of the Hypertension Unit, I described some of the antigens I was studying. My luncheon companion immediately recognized the importance of angiotensin antibodies in

physiologic and clinical studies and we decided to work on the problem of applying these antibodies to the assay of angiotensin peptides. The first fruit of this collaboration, a report of an immunoassay of angiotensin II, appeared in 1965.<sup>2</sup> Our interests then turned to measurement of the enzymatic activity of renin by determining the rate of generation of angiotensin I in plasma incubated in vitro. An angiotensin I antibody was developed by immunizing rabbits with this decapeptide coupled to poly-L-lysine. The assay itself was conventional and proved to be a remarkably straightforward and simple test. The method was reported together with a series of studies in normal human subjects, showing that plasma renin varied as expected with posture, sodium intake, and the administration of diuretics.

"Bernard Kliman and Andre Purnode were endocrinologists who helped us with the human studies on a metabolic ward. Theresa Koerner was a very skillful technical assistant.

"I believe the success of this publication relates to the fact that it represents the first report of a relatively simple method for assessing renin activity. It allowed the widespread application of renin measurement not only in research laboratories but also in hospital clinical laboratories. This method, with slight modification, is still widely used today. This work also illustrates how seemingly irrelevant basic science investigations may lead directly to valuable clinical insights, particularly when pursued in the appropriate environment.

"These early experiments with angiotensin peptides and their antibodies kindled my interest in the renin-angiotensin system; investigation in this area has continued actively in my laboratory. I shall receive the Volhard Award of the International Society of Hypertension in May of 1980 for "important contributions to the biochemistry and physiology of renin and the pathophysiology of hypertension."

1. **Haber E, Richards F F, Spragg J, Austen K F, Vallotton M & Page L B.** Modifications in the heterogeneity of the antibody response. *Cold Spring Harbor Symp.* **32**:299-310, 1967.
2. **Haber E, Page L B & Jacoby G A.** Synthesis of antigenic branch-chain copolymers of angiotensin and poly-L-lysine. *Biochemistry* **4**:693-8, 1965.