

This Week's Citation Classic

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Brunner H R, Laragh J H, Baer L, Newton M A, Goodwin F T, Krakoff L R, Bard R H & Bühler F R. Essential hypertension: renin and aldosterone, heart attack and stroke. *N. Engl. J. Med.* 286:441-9, 1972.
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In a retrospective analysis of 219 patients with essential hypertension, heart attacks and strokes were observed when plasma renin activity was normal or high, but in no instance when it was low. It was concluded that renin may be a risk factor in these patients. [The SCI® indicates that this paper has been cited in over 465 publications since 1972.]

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"Essential hypertension has long presented a puzzle to investigators. First results of measurements of plasma renin activity in these patients had been a disappointment insofar as they were rarely elevated.¹ Indeed most patients had seemingly normal, and a sizable fraction even subnormal, levels. However, those patients with low renin levels were most intriguing to us. We were convinced that widely varying renin levels must reflect basic differences among the patients and therefore we decided to review retrospectively all hypertensive patients who had been studied by J.H. Laragh's group at the Columbia-Presbyterian Medical Center during the years before renin measurements had become possible.

"After months of searching through charts and compiling data, I stumbled over the fact that none of the 59 low renin patients had suffered a severe cardiovascular complication such as heart attack or stroke. Since angiotensin, the vasoactive hormone produced by renin, had previously been shown

experimentally to elicit vasculotoxic effects, it seemed to make sense that the level of renin measured in hypertensive patients had some prognostic value. Together with Laragh, who happened to come by that Saturday morning, we were very excited about this observation and new concept.

"During the weeks that followed, while the manuscript was prepared, submitted to the *New England Journal of Medicine*, and finally in press, we were concerned that many other investigators may have made the same, what by then seemed to us obvious, observation and that the reaction at the time of publication would be, 'We have known this for a long time.' Our worries proved completely unnecessary, since the reaction of our peers was rather one of disbelief and eagerness to prove that we were wrong. Conceivably, it is largely based on this negative reaction that the paper has become a *Citation Classic*. Thus, I fear that if one analysed all individual citations, one would find that a large majority have referred to the paper in disbelief.

"The study was carried out retrospectively as were most of the studies which followed attempting to disprove the concept that renin may be a risk factor in patients with essential hypertension. Ten years later, the decisive prospective study still does not exist. Over the years, while many have challenged the idea, there has also been increasing support coming from experimental and clinical studies.² Perhaps more importantly, the provocative nature of our findings had triggered at the time a lot of new interest and research, trying to elucidate the role of the renin system in essential hypertension. This has, among other results, produced a new specific treatment for the disease by the development of inhibitors of the renin system."³

1. Helmer O M. Renin activity in blood from patients with hypertension. *Can. Med. Ass. J.* 90:221-5, 1964.
2. Gavras H, Brunner H R & Laragh J H. Renin and aldosterone and the pathogenesis of hypertensive vascular damage. *Progr. Cardiovasc. Dis.* 17:39-49, 1974.
3. Ondetti M A, Rubin B & Cushman D W. Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* 196:441-4, 1977.