

This Week's Citation Classic

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Laragh J H, Angers M, Kelly W G & Lieberman S. Hypotensive agents and pressor substances: the effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. *J. Amer. Med. Ass.* **174**:234-40, 1960. [Depts. Med., Obstet., and Gynecol. and Biochem., College of Physicians and Surgeons, Columbia Univ. & Presbyterian Hosp., NY]

Of a number of vasoconstrictors infused into volunteers, only angiotensin (the substance released by the kidney enzyme renin) stimulated aldosterone secretion. This revealed a kidney-adrenal biochemical 'axis' for control of sodium and potassium balance and blood pressure, and indicated that its derangement can cause malignant hypertension, with aldosterone excess and hypokalemia. [The *SCI*[®] indicates that this paper has been cited over 385 times since 1961.]

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"This paper, demonstrating the chemical interaction between the kidney and the adrenal cortex, was a keystone in the research journey that first exposed the renin-angiotensin-aldosterone hormonal 'axis' as a true biological control system for regulating simultaneously sodium and potassium homeostasis and blood pressure and tissue perfusion. The paper then showed its involvement in hypertensive diseases. We focused on how aldosterone regulates the amount of body sodium and water and had demonstrated that plasma potassium levels regulate aldosterone secretion. Observing hypokalemia in patients with malignant hypertension, we showed it was due to massive oversecretion of aldosterone. This was the first biochemical abnormality of causal relevance to be revealed in human hypertensive disease. We reasoned that the aldosterone excess might be caused by damaged kidneys. The renal enzyme, renin, was in disrepute as a biologically relevant substance. But its active product, angiotensin, had recently been synthesized, so we decided to see if it could affect aldosterone. By infusing angiotensin into

volunteers, we demonstrated that angiotensin II, unlike other pressor agents, sharply stimulated aldosterone secretion. Thus, a new hormonal link was established, with angiotensin (like K +) emerging as the second major stimulus for aldosterone secretion. The outlines of a new control system became apparent and we proposed that a disorder of it, with excesses of renin and aldosterone, caused malignant hypertension.

"Reasoning teleologically (i.e., if this is an organized system what are its purposes?) we detailed the normal, coherent regulation of sodium and potassium balance, arterial pressure, and tissue flow by the renin axis. We showed that derangements of the system either cause, sustain, or react to all naturally-occurring hypertensive disorders.

"Using the plasma renin activity, indexed against the 24 hour excreted sodium (renin profiling), derangements of the renin axis were defined in malignant hypertension, primary aldosteronism, oral contraceptive hypertension, and renovascular hypertension. We then showed that essential hypertension is not all alike, its different renin profiles expressing different mechanisms that respond to different treatments. In parallel, using pharmacologic probes, renin activity was shown to sustain part or all of the high blood pressure in some 70% (high and 'normal' renin forms) while its activity is virtually absent in another 30% with low-renin disease. This provided the basis for an all-encompassing vasoconstriction-volume hypothesis, viewing all hypertension as a spectrum ranging between excess vasoconstriction and excess volume. Renin profiling differentiates patients diagnostically and allows selection of lesion specific therapy. This research laid the foundation for the modern analysis and treatment of one of man's most life-limiting disorders.

"To me the three essential ingredients for such discoveries are a capacity to (1) recognize unusual clinical phenomena, (2) develop an hypothesis to explain the anomaly and design studies to test it, using (3) technically impeccable measurements. Without all three, discovery is unlikely."