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This Week's Citation Classic

Conn J W, Cohen EL & Rovner D R. Suppression of plasma renin activity in primary aldosteronism; distinguishing primary from secondary aldosteronism in hypertensive disease. *J. Amer. Med. Ass.* **190:**213-21, 1964.

Hypertension associated with overproduction of aldosterone, the salt-active adrenal hormone, results from either an abnormality of the adrenal gland itself or a circulatory deficiency of the kidney. This paper demonstrates that these two causes of hypertension can be distinguished functionally by measuring the level of plasma renin activity, subnormal in adrenal cases and supernormal in renovascular cases. [The *SCI*® indicates that this paper has been cited 276 times since 1964.]

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"We are delighted that one of our publications is included on the list of 'most cited papers.' Its review has awakened memories of excitement that my collaborators and I experienced as the data accumulated. It also recalled exciting earlier work which constituted the impetus for the 'most cited paper.'

"In 1954, after eight months of continuous and intensive study of a single patient, I had come to a novel conclusion: this hypertensive patient was suffering from a hitherto unrecognized disease due to excessive production of a then recently discovered hormone, aldosterone. I now faced two immediate problems: (1) to advise the patient to undergo surgical adrenal exploration and (2) to persuade a surgeon to do the operation. This kind of surgery had always been done for other purposes and with an entirely different constellation of biochemical indications. 'Can you justify this approach to the treatment of your patient? Is this an experiment?' asked the surgeon. I was floored, but I explained patiently again the important aspects of my data

"In the operating room I watched as the surgeon, through a deep incision, was palpating the right adrenal gland. He turned and said quietly, 'I can feel a small tumor in the gland and it bulges on the surface.' I stepped off my lift, aware that my head was suddenly full and pounding. I recall thinking, 'This will not be the last one.' Two weeks later my patient was cured. I called the disease Primary Aldosteronism (PA). Since then, thousands of such patients throughout the world have undergone similar operations.

"Now back to the 'most cited paper.' By 1961 the renin-angiotensin system had been linked to aldosterone production. Reno-vascular hypertension (RVH), associated with aldosteronism, now had a clear explanation: excessive renin-angiotensin production with stimulation of too much aldosterone from *normal* adrenals (secondary aldosteronism). How could we distinguish between these two forms of hypertension, each associated with excessive production of aldosterone? I was aware of a 1957 report by F.W. Dunihue and W.V.B Robertson demonstrating atrophy of renal juxtaglomerular cells (site of renin production) following administration of des-oxycorticosterone, a steroid with properties similar to those of aldosterone.[1] This proved to be the key. It suggested that renin production might be very low in PA and, indeed, it was. By a then crude bioassay we could measure the range of renin activity in normal people and the very high levels in RVH. But we could detect none in PA. A clear functional distinction was now established. It was evident also that angiotensin was not involved in the genesis of the hypertension of PA. We now recognized low-renin and high-renin forms of human hypertension. The need for hypertension researchers to study the low end of the renin scale, as well as the high, became evident."

REFERENCE

1. Dunihue F W & Robertson W V B. Effect of desoxycorticosterone acetate and of sodium on juxtaglomerular apparatus. *Endocrinol.* **61:**293-7, 1957.