This Week's Citation Classic®

Kagawa C M, Sturtevant F M & Van Arman C G. Pharmacology of a new steroid that blocks salt activity of aldosterone and desoxycorticosterone. *J. Pharmacol. Exp. Ther.* 126:123, 1959.
[G.D. Searle & Co., Chicago, IL]

This paper summarized the preclinical pharmacology of a new steroid from a novel series, the spironolactones, which were found to block the renal effects of mineralocorticoids and, independently, to reduce blood pressure in experimental hypertension. Subsequently, the steroid was modified by insertion of a 7 α-acetylthio radical to improve oral activity and was marketed by Searle as Aldactone (spironolactone) and Aldactazide (spironolactone with hydrochlorthiazide). [The *SCI*® indicates that this paper has been cited in more than 100 publications.]

A Lesson to Be Gained from Basic Research Programs

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In the 1950s, biologists at Searle were allowed to devote 50 percent of their time to research of their own choosing. Thus, when top management decided that there was no more interest in the pharmacologic screening of the spironolactone series synthesized by Jack A. Cella and Bob C. Tweit,[1,2] for reasons of our own, we independently chose to transfer our activities with this interesting series of compounds to our respective basic research programs.

I was in charge of the antihypertensive program that I had inherited from the late Dan Green, former director of the biology division, when he left Searle. I was continuing the research on experimental mineralocorticoid and renal hypertension and had begun to develop a strain of spontaneously hypertensive rats. (Incidentally, contrary to the recent representation by K. Aoki,[3] this was the first such endeavor and had been demonstrated by me along with my concept of the polygenic inheritance of blood pressure homeostasis. I had published my initial breeding results in 1953.[4] Unfortunately, my breeding colony was wiped out a year or so later by a midnight flood in the animal room, and a substrain I had sent to Hans Selye's lab in Montreal was discontinued on the departure of colleagues there.)

As I investigated an interesting member of the spironolactone series dubbed SC-5233, I found it to have intrinsic antihypertensive activity in rats receiving desoxycorticosterone acetate (DCA) and in rats with established, post-DCA, or metacorticoid, hypertension.[5,6] This activity was separable from the antimineralocorticoid activity of the steroid at the renal level.[6] This was later confirmed in clinical investigations with spironolactone itself.

Charlie M. Kagawa, working in the renal labs of Gordon Van Arman, had been seeking anti-OCA candidates for use in the treatment of edematous states. Quite independently, he had become intrigued with the blocking activity of SC-5233 against the sodium-retaining action of DCA and aldosterone.[7]

The biology group at Searle in those days was small, and we customarily ate lunch together at a single table. Charlie, Gordon, and I shared our findings over sandwiches and, subsequently, recommended to management that SC-5233 be developed as a candidate for clinical trial. This was accepted and clinical confirmation was soon forthcoming.[6] We pooled our data and published our now-*Classic* paper in June 1959.

I left Searle in 1958, followed by Kagawa and Van Arman somewhat later. However, Cella's compounds were restored to the screening programs and the 7α-acetylthio derivative was synthesized and eventually marketed for the treatment of essential hypertension, primary hyperaldosteronism, and various edematous conditions.

Why has this article been frequently cited? I can only hypothesize that it is because this was the first discovery of a steroid with clinically confirmed antihypertensive and antialdosterone activity. Aldactone (spironolactone) remains on the market today, over three decades later, as a product of our basic research programs.

My thanks to Kagawa and Van Arman for their comments on this note.

1. **Cella J A & Kagawa C M.** Steroidal lactones. *J. Amer. Chem. Soc.* 79:4808-9, 1957.
2. **Cella J A & Tweit R C.** *Alkanoylthio-17α-carboxyethyl-17B-hydroxyandrosten-3- one lactones.* US Patent 3,013,012.
3. **Aoki K.** From a new apparatus to a new strain of rats. Citation Classic. Commentary on *Jpn. Circ. J.* 27:282-93, 1963. (Cited 1,380 times.) *Current Contents /Life Sciences* 33(48):19. 26 November 1990.
4. **Sturtevant P M.** Artificial selection program for degenerative diseases in rats. *Genetics* 38:696. 1953.
5. ---------- Anti-hypertensive effects of an aldosterone antagonist. *Fed. Proc.* 17:413, 1958.
6. ---------- . Anti-hypertensive effects of an aldosterone antagonist. *Science* 127:1393-4, 1958.
7. **Kagawa C M. Cella J A & Van Arman O G**. Action of new steroids in blocking effects of aldosterone and deoxycorticosterone on salt. *Science* 126:1015-6, 1957. (Cited 270 times.)
8. **Liddle G W.** Sodium diuresis induced by steroidal antagonists of aldosterone. *Science* 126:1016-8, 1957. (Cited 175 times.)

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