CC/NUMBER 26
JULY 1, 1991

This Week's Citation Classic®

de Bold A J, Borenstein H B, Veress A T & Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci.* 28:89-94, 1981. [Depts. Pathol. and Physiol., Univ. Ottawa and Ottawa Heart Inst., Ottawa Civic Hosp., Ontario; and Dept. Physiol., Univ. Toronto, Ontario, Canada]

This paper established that heart atrial extracts, unlike ventricular ones, contain a powerful natriuretic factor that also lowers blood pressure and increases hematocrit values. This finding was deemed related to the existence of secretory-like granules in atrial cardiac muscle cells and was compatible with an endocrine function for the heart. [The *SCI*® indicates that this paper has been cited in more than 1,525 publications.]

The Discovery of Atrial Natriuretic Factor

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In 1968, shortly after graduating, my wife and I moved from Argentina to Canada. Within our first year at the Department of Pathology at Queen's University, I became strongly attracted to a project aimed at unraveling the function of storage granules present in atrial cardiocytes of mammals, or "specific atrial granules." Morphologically, these granules resemble storage granules found in endocrine cells known to produce polypeptide hormones. This morphological finding was a challenge to the well-established concept that cardiac muscle cells are mostly differentiated for excitation, contraction, and conduction, but not for secretion. In addition, it was thought that cells that produce polypeptide hormones derive from the neural crest—an embryological origin not shared with cardiac muscle cells.

During a 10-year period, our group developed technologies to isolate the atrial granules and to stain them at the light microscopic level. This, in turn, allowed us to perform systematic histochemical, biochemical, and morphometric investigations on the atrial granules. By the late 1970s, our lab's hypothesis was that atrial granules were storage particles containing basic polypeptides with a random coil conformation, high turnover rate, and histochemical properties compatible with the presence of sulfur- and indole-containing amino acids (all later confirmed biochemically). The morphometric method allowed for unbiased measurements of the degree of granularity of the atrial muscle and for testing several experimental procedures reported to alter the number of granules in the rat atrium. We found unequivocal changes with some procedures known to alter water and electrolyte balance.

A target for a secretory product with a role in maintaining water and electrolyte balance was the kidneys. Together with H. Sonnenberg, we tested this hypothesis by injecting saline extracts of rat atria muscle into bioassay rats. We observed a very powerful diuretic and natriuretic effect as well as a decrease in blood pressure and in hematocrit values. These results were described in the paper that is the subject of this commentary.

There are at least three primary reasons for this paper's status. First, the concept that the heart has an endocrine function was astonishing. Second, the published experiments were as reproducible as they were dramatic. To be convinced of the diuretic effect, one had only to watch the urine output from test rats go from one or two drops per minute to a steady stream immediately following the injection of the atrial extracts. Third, the discovery of an "atrial natriuretic factor" (ANF)[1] brought a fresh new endocrine parameter to the attention of the many basic and clinical scientists interested in blood volume, pressure regulation, high blood pressure, and chronic congestive heart failure. Several groups in these fields were well positioned to try to unravel the physiological and pathophysiological significance of the new hormone.

As investigations progressed, interest escalated because the ANF discovery opened the door to new biological insights.[2] These included the modulating actions of ANF on the renin-angiotensin-aldosterone system and the finding that many biological actions of ANF are mediated, at the cellular level, by the interaction of ANF with guanilyl cyclase. This provided an unexpected but key function for the sedimentable form of this enzyme that, surprisingly, turned out to be an ANF receptor as well.[3]

The ANF discovery also led to the finding that there are natriuretic peptides and that extracardiac sources of these peptides likely indicate autocrine or paracrine functions related not only to blood volume regulation but to as yet undetermined physiological functions.

1. de Bold A J. Atrial natriuretic factor: a hormone produced by the heart. *Science* 230:767-70, 1985. (Cited 360 times.)
2. de Bold M L & de Bold A J. Effect of manipulations of Ca^{+2} environment on atrial natriuretic factor release. *Amer. J. Physiol.* 256:H1588-94, 1989.
3. Chinkers M, Garbers D L, Chang M S, Lowe D G, Chin H M, Goeddel D V & Schulz S. A membrane form of guanylate cyclase is an atrial natriuretic peptide receptor. *Nature* 338:78-83, 1989. (Cited 120 times.)

Received November 19, 1990