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Flynn T G, de Bold M L & de Bold A J. The amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. *Biochem. Biophys. Res. Commun.* 117:859-65, 1983.
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This paper describes, for the first time, the purification and amino acid sequence of atrial natriuretic peptide, a 28 amino acid, disulfide bonded peptide from heart atria with potent diuretic and natriuretic properties. [The *SCI*® indicates that this paper has been cited in more than 560 publications.]

Atrial Natriuretic Peptide

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My involvement with atrial natriuretic peptide began in the fall of 1981 when Adolfo de Bold, then in the Department of Pathology at Queen's University, asked me to help him identify and characterize a substance, present in heart atria, that he had termed atrial natriuretic factor (ANF). Earlier in 1981, de Bold, in collaboration with Harold Sonnenberg at the University of Toronto, had injected saline extracts of rat atria into bioassay rats.[1] This produced a massive diuresis, natriuresis, and fall in blood pressure, demonstrating that heart atria contained a substance or substances which, if secreted from the heart, could play a role in the regulation of extracellular fluid volume and blood pressure.

I was not at all familiar with this field when first approached by de Bold. I was, by training, an enzymologist, and I had just begun to get into the area of protein structure by means of protein sequencing. De Bold had, through earlier studies,[2] obtained evidence that the natriuretic factor was a peptide or protein. Even though I was not familiar with the ANF field, I was very much taken with the story he laid before me, and I was excited that we might be the first to demonstrate that the heart was an endocrine organ.

One of the problems at the outset was lack of money to do this research. Our initial attempts to obtain funding through granting agencies did not meet with much success, and I was very surprised at not only the apathy that we encountered but also the skepticism with which this problem was being viewed by many people, including those in the field of renal and cardiovascular physiology. However, we did manage to obtain some funding, and the first homogeneous preparation of a diuretic peptide was obtained, by de Bold, by a combination of traditional purification methods and HPLC.[3] The presence of cystine in the amino acid composition of this material gave clear indications that it contained a disulfide bond. Our first sequencing attempts resulted in the identification of the first 24 amino acids and the positions of the Cys residues. Subsequently, we sequenced the whole molecule.

The results were published in the fall of 1983, and it was the first published account of the sequence of atrial natriuretic peptide—which is why, I believe, it has been cited frequently. It was followed quickly by papers from other groups that confirmed our original findings.[4,5]

The sequencing of atrial natriuretic peptide was a salutary experience because it introduced me, for the first time, to the cutthroat competition of a fast moving field. I realized from the very beginning that the concept that the heart was an endocrine organ would have major implications and produce a flurry of activity. I did not realize, however, that it would produce the number of papers and reviews[6] that have been written since we began the work.

By 1981, there were perhaps a dozen papers relating to ANF. A decade later, more than 4,000 have been published. The intriguing feature of all of this work is that, despite this enormous amount of activity, the precise role of atrial natriuretic peptide in the control of body fluid and blood pressure remains elusive.[6]

Adolfo de Bold received numerous well-deserved awards for his discovery of ANF, but it was gratifying for me to share the 1986 Gairdner International Award with Sonnenberg and de Bold for our combined efforts in characterizing the peptide.

1. **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. (Cited 1,670 times.) [See also: **de Bold A J.** Citation Classic. *Current Contents/Life Sciences* 34(26):8, 1 July 1991.]
2. **de Bold A J.** Atrial natriuretic factor of the rat heart. Studies on isolation and properties. *Proc. Soc. Exp. Biol. Med.* 170:133-8, 1982. (Cited 160 times.)
3. **de Bold A J & Flynn T G.** Cardionatrin 1—a novel heart peptide with potent diuretic and natriuretic properties. *Life Sci.* 33:297-302, 1983. (Cited 130 times.)
4. **Currie M G, Geller D M, Cole B R, Siegel N R, Fok K R, Adams S P, Eubanks S T, Galluppi G R & Needleman P.** Purification and sequence analysis of bioactive atrial peptides (atriopeptins). *Science* 223:67-9, 1984. (Cited 515 times.)
5. **Kangawa K & Matsuo H.** Purification and complete amino acid sequence of a-human atrial natriuretic polypeptide (a-hANP). *Biochem. Biophys. Res. Commun.* 118:131-9. 1984. (Cited 660 times.)
6. **Brenner B M, Ballerman B J, Gunning M E & Zeidel M L.** Diverse biological actions of atrial natriuretic peptide. *Physiol. Rev.* 70:665-99, 1990.

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