This article was the first statement of the "Na pump inhibition (natriuretic hormone)-Na/Ca exchange-hypertension hypothesis." The hypothesis explains how the tendency to retain sodium ultimately causes the elevation of blood pressure in humans (and animals) with salt-dependent hypertension. (The SCI indicates that this paper has been cited in over 840 publications.)

The seeds for this article were sown in 1971, when Harold Reuter invited me to spend the summer in Bern, Switzerland; we agreed to explore the possible role of Na/Ca exchange in the control of intracellular Ca2+ in vascular smooth muscle. My ideas about its potential relevance to hypertension began to gel when I was invited to present an Introductory Lecture at one of the sessions of the 1976 Federation of American Societies for Experimental Biology meeting. I decided to speak about Na/Ca exchange in various types of muscle.

In reviewing the smooth muscle data and my data from crustacean muscle, I was struck by the evidence that the vascular muscle contracted in response to much smaller reductions in the Na+ gradient than did barnacle muscle. This led me to realize that, in smooth muscle cells with maintained tone, the cytosolic free Ca2+ concentration must always be maintained above the contraction threshold (in contrast to skeletal muscles, which relax completely between twitches). I concluded that the Ca2+ gradient across the plasma membrane must be modulated and that Na/Ca exchange participate in this modulation. This provided a direct link between Na+ metabolism and vascular contractility (and blood pressure). I then tried to think of ways that excess dietary Na+ and renal Na+ retention might lead to an elevation of intracellular Na+ (and thus, via Na/Ca exchange, to an increase in cell Ca2+).

A review of the literature convinced me that the postulated natriuretic hormone ("third factor"), which appeared to behave like an "endogenous digitalis," fit as a missing link in the chain between retention of Na+ and elevation of cell Ca2+. Na+ retention and plasma volume expansion should trigger the secretion of this hormone, the hormone's direct natriuretic action, as well as the pressure-induced natriuresis, should compensate for the tendency to volume expansion. I discussed my ideas with Paul DeWeer, who encouraged me to prepare an article on this subject for the new "Cell Physiology" section of the American Journal of Physiology (Paul was a member of the editorial Board).

While my article was in press, F.J. Haddy and H.W. Overbeck's review on volume-expanded hypertension appeared; they, too, invoked an "endogenous digitalis," but did not mention Na/Ca exchange. H.E. deWardener and G.A. MacGregor pointed out that Louis K. Dahl had first suggested (in 1969) that a "sodium-excreting (natriuretic) hormone with hypertensiveogenic capacity" appeared to play a role in the pathogenesis of salt-dependent hypertension.

The "natriuretic hormone-Na/Ca exchange-hypertension hypothesis" has been subjected to extensive testing during the past decade. There is evidence that many individuals with salt-dependent hypertension have a tendency to retain Na+ and to expand blood volume. The search for the elusive "endogenous digitalis," which appears to be present in relatively high concentrations in the plasma of individuals with low-renin essential hypertension, may be reaching a climax with the recent report of its purification. The physiological significance of Na/Ca exchange in the regulation of vascular smooth muscle cell Ca2+ has been controversial. However, recent studies clearly show that vascular smooth muscle, like most other types of muscle, contains a large-capacity Na/Ca exchanger that plays an important role in cell Ca2+ regulation, especially when cytosolic free Ca2+ exceeds the contraction threshold.

The seminal influence on my thinking was the aforementioned contrast between vascular smooth muscle and barnacle muscle Ca2+ metabolism. I am especially grateful to the American Heart Association for the grant-in-aid that supported my early work on barnacle muscle. Who would have thought that this seemingly esoteric research would lead to a new view of the pathogenesis of salt-dependent hypertension? It now gives me great pleasure to try to repay my debt to the Heart Association by serving as a member of its Research Committee.