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# This Week's Citation Classic®

**Coleman T G & Guyton A C.** Hypertension caused by salt loading in the dog. III. Onset transients of cardiac output and other circulatory variables. *Circ. Res.* **25**:153-60, 1969.
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Subtotal nephrectomy and increased dietary sodium were combined to produce hypertension in the dog. A transient increase in cardiac output at the onset of hypertension preceded an increase in vascular resistance. This temporal relationship suggested that autoregulatory vasoconstriction might be responsible for the hypertension. [The *SCI*® indicates that this paper has been cited in over 200 publications since 1969.]

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There were no reliable experimental models of hypertension in the early 1900s. Then, in 1934, Goldblatt and colleagues[1] showed that partial renal artery constriction would produce hypertension in the dog. Innumerable experiments and theories have subsequently attempted to connect initial renal insult with an eventual generalized peripheral vasoconstriction. One theory begins with the writings of Ernest Starling, who described interactions among body fluids, hemodynamics, and kidney function in 1909;[2] these ideas have become a fundamental part of the infrastructure of contemporary cardiovascular physiology. Bayliss had introduced the idea of autoregulatory vasoconstriction in 1902.[3]

In the early 1960s, Ledingham and Cohen[4,5] and Borst and Borst-de Geus[6] built on these ideas and applied them to the genesis of hypertension. I originally thought that the Borsts' concepts were a bit ambiguous, but in retrospect they appear to be a model of clarity. The gist of the theory is that disruption of sodium balance is an important component of the onset of hypertension. Renal insult decreases sodium excretion; retained sodium in the form of increased plasma volume forces an increase in cardiac output; elevated flow triggers autoregulatory vasoconstriction; vasoconstriction raises arterial pressure, which improves sodium excretion and reestablishes sodium balance. The price is hypertension.

It had previously been shown that subtotal nephrectomy plus increased sodium intake produces a distinct but reversible hypertension associated with sodium retention. One of the charms of this model is that the renin-angiotensin system is suppressed; this avoids the ambiguities of Goldblatt's model wherein both elevated renin levels and sodium retention are implicated. I was a graduate student in the mid-1960s, and Arthur Guyton was my mentor. We built a mathematical model[7] based on the theory outlined above, and it predicted that a transient increase in cardiac output would occur over about a week at the onset of nephrectomy-salt hypertension. Thus, a natural experiment was to look for the transient in the experimental model. We looked and we found it. This was not a definitive test of the theory, but the temporal relationship between cardiac output and total peripheral resistance did suggest that a generalized autoregulatory response might be occurring. We missed the mark in one respect. Liard subsequently showed that it is only skeletal muscle (and not all of the tissues of the body) that participates in the observed hemodynamic response.[8]

The sodium retention-autoregulation theory, like many competing theories, is stuck somewhere between general acceptance and outright rejection. The genesis of hypertension—both experimental and clinical—is complex and often insidious. Definitive experiments are needed but are generally not possible.

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2. **Starling E H.** *The fluids of the body.* Chicago: Kenner, 1909. 186 p.
3. **Bayliss W M.** On the local reactions of the arterial wall to changes in internal pressure. *J. Physiology* **28**:220-31, 1902. (Cited 515 times since 1955.)
4. **Ledingham J M & Cohen R D.** Circulatory changes during the reversal of experimental hypertension. *Clin. Sci.* **22**:69-77, 1962. (Cited 95 times.)
5. ----------. Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* **1**:887-8, 1963.
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8. **Liard J F.** Regional blood flows in salt loading hypertension in the dog. *Amer. J. Physiol.* **240**:H361-H367, 1981.

 