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This Week's Citation Classic®

de Wardener H E & MacGregor G A. Dahl's hypothesis that a saluretic substance may be responsible for a sustained rise in arterial pressure: its possible role in essential hypertension. *Kidney Internal.* 18:1-9, 1980.
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This paper brought together evidence to support a coherent hypothesis to explain the development of essential hypertension. We suggested that a genetic defect in the kidney's ability to excrete sodium stimulates compensatory mechanisms to prevent sodium retention and that eventually one or more of these adaptations cause a rise in arterial pressure. [The SC®/ indicates that this paper has been cited in more than 415 publications.]

Essential Hypertension, Kidney, Sodium: A Hypothesis

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For some years we had been working on mechanisms controlling sodium excretion and the importance of salt intake on blood pressure. One substance that was then considered to be of potential importance in controlling sodium excretion was an inhibitor of Na-K-ATPase, the plasma concentration of which was known to be altered by changes in sodium intake. It was thought that the plasma concentration of this substance is increased in experimental forms of hypertension.[1,2]

Central to the evolution of the hypothesis were the fundamental kidney cross-transplantation experiments that demonstrate that in inherited hypertension in rats and possibly in essential hypertension in man, the hypertension is primarily due to a genetic defect in the kidney.[3] Other evidence suggested that this abnormality expresses itself as a difficulty in excreting sodium.[4] We were also aware of both F.J. Hacidy's[2] and M.P. Blaustein's[5] suggestion that an increase in a circulating Na-K-ATPase inhibitor might raise the blood pressure. In addition we had recently found that the plasma's ability to inhibit Na-K-ATPase is increased in essential hypertension.

Bringing these strands together in a unifying hypothesis was exhilarating, as these and other disparate aspects of hypertension increasingly fell into place. It is probable that our paper has been quoted so often because it brought all these abnormalities together into a coherent scheme. This was made easier by pointing out that in essential hypertension the mechanisms needed to overcome a persistent restraint on the excretion of a normal sodium intake, due to the presence of an abnormal kidney, were equivalent to those involved in excreting a raised sodium intake in the presence of a normal kidney.

The paper was difficult to publish and it took two years before it was, almost as a favour! It was remarkable, however, that two years later an updated shortened version was accepted by Lancef in 1982,[6] and that the next year a much expanded and more comprehensive version, which brought in many aspects of hypertension of which we had previously been unaware, was published in *Medicine.*[7] A review of additional evidence in favour of the hypothesis, which had accumulated since 1983, was published in 1990.[8,9]

1. **Schmidt R W, Bourgoignie J J & Bricker N.** On the adaptation in sodium excretion in chronic uraemia *J. Clin. Invest.* 53:1736-41, 1974 (cited 60 times.)
2 **Haddy F J & Overbeck H W.** The role of humoral agents in volume expanded hypertension. *Life Sci.* 19:935-48. 1976. (Cited 320 times.)
3. **Dahl L K & Heine M.** Primary role of renal homografts in setting chronic blood pressure levels in rats. *Circ. Res.* 36:692-6. 1975. (Cited 170 times.)
4. **Tobian L, Lange J, Azar 5, Iwai J, Koop D, Coffee K & Johnson M A.** Reduction of natnuretic capacity and renin release in isolated, blood-perfused kidneys of Dahl hypertension prone rats *Circ. Res.* 43(Supp. 1):I92-8. 1978 (Cited 135 times)
5. **Blaustein M P.** Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis *Amer. J. Phvsiol.* 232:C 165-73, 1977 (Cited 1,050 times.) (See also: Blaustein M P. Citation Classic. *Current Contenlst®/Life Sciences* 31(47): 16. 21 November 1988]
6. **de Wardener HE& MacGregor G A.** The natriuretic hormone and essential hypertension L*ancet* 1:1450-4. 1982 (Cited 100 times.)
7.---------- . The relation of a circulating sodium transport inhibitor (the natnureue hormone) to hypertension. *Medicine* 62:310-26. 1983. (Cited 125 times.)
8 **de Wardener H** E. The primary role of the kidney and salt intake in the aetiology ot essential hypertension Part I *Clin Sci.* 79:193-200. 1990.
9 ---------- . The primary role of the kidney and salt intake in the aetiology of essential hypertension Part II *Clin. Sci.* 79:289-97.1990

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