

This Week's Citation Classic

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de Wardener H E, Mills I H, Clapham W F & Hayler C J. Studies on the efferent mechanism of the sodium diuresis which follows the administration of intravenous saline in the dog. *Clin. Sci.* **21**:249-58, 1961.
(Dept. of Medicine and the Isotope Lab., St. Thomas's Hospital and Medical School, London)

Dogs loaded with sodium-retaining and antidiuretic hormones were given a rapid saline infusion intravenously. Increased sodium excretion occurred with lowered filtration rate and renal denervation. Cross circulation between infused and non-infused dogs suggested the presence of a natriuretic hormone with a short half-life. [The *SCI*[®] indicates that this paper has been cited over 300 times since 1961.]

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"In 1958 when I returned from working at the National Institutes of Health, Bethesda, on the afferent pathways in the regulation of aldosterone secretion, de Wardener was then working on the excretion of dilute urine in dogs loaded with antidiuretic hormone. I suggested that it might be related to the effect of the volume expansion on the rate of aldosterone secretion. He invited me to join him. We loaded dogs with sodium-retaining hormone (fluorocortisone), and studied sodium excretion.

"In our paper there were two sets of experiments which probably account for the frequency of citation of the paper. The first set dealt with the excretion of an infused saline load while the glomerular filtration rate was decreased. This we achieved by in-

flating a balloon in the aorta so that the pressure at the renal arteries was lowered to 90 mm Hg.

"The importance of this series of experiments was that it was the first time that a marked increase in sodium excretion had been produced while the glomerular filtration rate and, therefore, the rate at which sodium was filtered, was reduced to well below the rate of filtration during the pre-infusion period. Prior to that it had been argued—and even today some people still stick to the argument—that changes in filtration rate which were too small to be measured by available techniques could explain the increases in sodium excretion.

"The second set of experiments which were very important were those in which cross-circulation between two dogs was effected. One dog was on a beam balance and so could have its weight controlled during cross-circulation; the other dog at the table then received a rapid saline infusion. Although the blood of the dogs rapidly became the same for a variety of factors, only the infused dog had a pronounced diuresis.

"We concluded, especially from these two sets of experiments, that the regulation of sodium excretion depends upon a change in the concentration of a circulating substance, other than aldosterone, which had a short half life. It was assumed that we had for the first time demonstrated that a circulating natriuretic hormone existed, though we were careful not to use that term. After that, people all over the world started looking for the natriuretic hormone. Time has shown that there is a linked series of natriuretic substances and that some of these originate in the kidney itself."